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THECA-CELL TUMOR OF OVARY IN CHILD ONE YEAR OF AGE

WITH REVIEW OF THE LITERATURE

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THE present report concerns a patient 1 year, 8 days of age with a theca-cell tumor of the left ovary, and a review of the literature regarding tumors of the ovary which are considered related histogenetically to the cells of the theca interna of the ovary or their precursors.

It is an accepted fact that ovarian tumors occur in childhood, but they are rare enough to be frequently overlooked. Ovarian tumors of the theca-cell type in a child only slightly over one year of age are exceedingly rare, since in a review of the literature of the last twenty years, no patient this young with this type of tumor was discovered. According to Dockerty,[1] 80 per cent of thecomas occur after the menopause, and produce vaginal bleeding which may not be periodic. Banner and Dockerty[2] as recently as 1945 stated that theca-cell neoplasm occurring in the first decade of life had been described. McGoldrick and Lapp[3] stated in 1944 that "65 per cent of the theca-cell tumors occur after the menopause, and 35 per cent in the period between puberty and the climacterium. The tumor has never yet been demonstrated in children." Our patient, to our knowledge, represents the first thecoma reported in the prepubertal age group.

In 1932, Loeffler and Priesel[4] first described a series of six patients with ovarian tumors containing thecal cells. In 1934, these same authors (see Chamsi[5]) added four more cases, and Melnick and Kanter[6] two cases. In 1935, Geist[7] added five more cases.

In a review of the literature for the last twenty years, the following reports of cases of tumors of the cells of the theca interna of the ovary have been found.

Year	*No. Cases*
1932 Loeffler and Priesel[4]	6
1934 Loeffler and Priesel[5]	4
1934 Melnick and Kanter[6]	2
1935 Geist[7]	5
1936 Brosig[5]	1
1937 Reopelle (cited by Varangot)[5]	1
1937 Patterson and McCullag[5]	1
1937 Neely[5]	1
1938 Geist and Gaines[8]	6
1938 Fischer[5]	1
1938 Huber[5]	1
1938 Hammar[5]	1
1938 Draganic[5]	2
1938 Mocquot, Moricard, and Mlle. Gothie[5]	1

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1938	Delarue and Isidor[5]	1
1939	Varangot and Monlonguet[5]	2
1939	Collins, Varino, and Weed[9]	2
1939	Greenblatt, Greenhill, and Brown[10]	2
1939	Peel[5]	1
1939	Ruzieska[5]	1
1940	Pallos[5]	2
1940	Traut and Marchetti[11]	4
1940	Treite[5]	2
1940	Dockerty[1]	10
1941	Curtis[12]	1
1941	Tailhefer[5]	1
1941	Sirtori and Bussolati[13]	1
1942	Danforth[14]	1
1945	Banner and Dockerty[2]	13
1946	Guèrin, P, Guèrin, M., and Tailhefer[5]	20
1947	Limburg[15]	7
1947	Chamsi[5]	3
1948	Knight[16]	15
1948	Gregoire[17]	2
1948	Gucnin and Messimy[18]	1

With our case, the number reported which we found in the literature of tumors of the theca interna of the ovary is 126. The only case we found in the literature which at all approximates the youth of the child under discussion is that reported by Limburg.[15] His patient was a 2-year, 3-month-old white girl who came to the University Women's Clinic in Hamburg-Eppendorf. For four days previously, she had had a bloody vaginal discharge, and prior to this the mother had noticed the breast development of the child.

Physical examination of this child revealed an abdominal tumor "the size of a child's head,"[15] a considerable development of the breasts, and light pubic hair. From the swollen vagina, there was a serosanguineous discharge.

Operation revealed a turgid elastic tumor 17 × 11 × 9 cm. arising from the left ovary. The right ovary was entirely normal. The uterus and tubes were proportionately enlarged. The tumor was cystic, smooth-walled, of a grayish color. Histologically, there was no normal ovarian tissue to be seen. In sections of the solid tumor parts with Mallory's stain, granulosa cells and thecal cells were present in equal proportions, whereas most of the rest of the tumor was composed of granulosa-like constituents. Fat stains showed diffuse, fine, droplet-like lipoid within the cells, especially in the theca-cell part. No reticulum stains were done.

It would appear from the description of this tumor that it was predominantly of the granulosa-cell type, although it contained some theca-cell elements. Certainly the picture was quite different from that presented by the tumor described in this paper.

It is probable that thecomas may occur at any age. The oldest patient reported that we found in the literature was 92 years of age and the youngest 16 years,[3] with the exception of Limburg's case (which is a mixed tumor of the ovary), and the one added in this paper. Some theca-cell tumors are biologically active as evidenced by atypical bleeding.

Theca-cell tumors reported among patients of a younger age group have usually been associated with amenorrhea or with menometrorrhagia. The clinical picture may not be so uniform with this type of tumor as it is with the granulosa-cell tumor.

PATHOLOGY

Theca-cell tumors according to Collins, Varino, and Weed[9] vary in size from a few centimeters in diameter to the size of a large grapefruit, and their consistency on vaginal examination is that of a fibroma of the ovary or a fibromyoma of the uterus. The growth is irregular in outline and a yellowish brown to yellowish red color.

On cut-section the tumor is well encapsulated, and is composed of many islands of yellow tissue separated by bands of connective tissue. Occasionally, cystic areas exist throughout the tumor.

Microscopically, theca-cell tumors are made up of interlacing bands of spindle or epithelioid cells, irregularly distributed, and separated by strands of connective tissue containing hyaline plaques. The nuclei are oval or rod-shaped with an occasional mitotic figure present.

Fat stains show the presence of intracellular and extracellular lipoid material, which, according to Geist and Gaines,[8] is doubly refractile and probably consists of cholesterol or cholesterol esters.

Traut and Marchetti[11] reported that Foot's silver stain is most helpful in differentiating not only the cellular variations but also the relation of various cells to the reticular elements of the supporting connective tissue. These authors have given us a very good description of the differential points between thecal and granulosa cells. The granulosa cells, when present, occur in islands, consisting of from a few to several hundred cells. They seldom exist singly. The islands are surrounded by strands or networks of reticulum in which there are numerous thecal cells and the vascular supply. According to these authors, the nuclei of the thecal and granulosa cells are the same, but the cytoplasm of the granulosa cell contains many argentophilic granules whereas the cytoplasm of the thecal cell has almost none. The thecal cell is always in intimate relationship to the reticular framework to such a degree that each cell is surrounded by a capsule of this material which isolates it from its neighboring thecal cells. In contrast, the granulosa cells exist usually in large groups, each cell being in intimate contact with its neighboring granulosa cell. The complete island of granulosa cells is surrounded but not penetrated by the reticulum.

On the basis of the above pathological description, Traut and Marchetti[11] feel it is possible to analyze tumors of the graafian follicle as to their content of these two types of cells. Clinically, thecal tumors are unilateral and of the consistency of fibromas.

CASE REPORT

A white female, aged 1 year, 8 days, was seen by one of us (V. H. G.) for the usual well-baby examination at the end of a year. The mother did not bring this child in because she was particularly worried about her, except that she did casually mention that she thought it was peculiar that a 1-year-old child should have a white vaginal discharge. When the child was in the office at the age of 10 months, no such complaint had been made and no abnormal findings were noted on examination.

The mother's first pregnancy terminated in an abortion at three months. She was given progesterone while pregnant with the child who is the subject of this case report. The pregnancy terminated without mishap. The delivery was a normal one with the use of prophylactic forceps, and the child's condition was good at birth.

This child had been seen first in the office at 3½ months of age because of slight diarrhea, but there were no other abnormal physical findings at that time.

Growth and development up to the examination at 1 year, 8 days, was essentially normal except that the mother was distressed about her excessive diurnal activity and inability of the child to sleep.

Physical examination of this child at 1 year, 8 days, revealed a well-developed, very well-nourished female child who did not appear more mature than her chronological age. The obvious defects were an unusually protuberant abdomen, pigmented areolae of the breasts, and hypertrophy of both breasts to the size of half a medium lemon (Fig. 1). There was no

Fig. 1.—Photograph of the patient, aged 13 months, taken the day before surgery, showing the areolar pigmentation, breast enlargement, and protuberant abdomen.

axillary hair. The clitoris seemed larger than normal for this age and the labia majora and minora were definitely enlarged. The mucosa of the hymen was redundant (Fig. 2). The vaginal discharge was white and mucoid but not bloody. There were a few wisps of long black hair over the symphysis pubis.

A tumor mass about 3 × 3 cm. was felt in the right lower quadrant of the abdomen or in the midline, freely movable, smooth, hard, and nontender. It was difficult to ascertain if this mass were connected with the kidney. A vaginal examination was done easily with the little finger and a bimanual examination revealed a slightly enlarged uterus. There was no acne or abnormal hirsutism. The resting blood pressure was 85/60. Eye ground examination was negative. Dentition was not accelerated (teeth 3/2 all incisors).

The anterior fontanel was open 2 × 2 cm. X-ray of the skull was entirely normal with no change in the sella turcica.

Intravenous pyelograms were made and were essentially normal but the plates showed a relative absence of gas in the mid-abdomen which suggested a space-occupying lesion.

An analysis for bone age was made and, "on these films, it is evident that the proximal epiphyses of the phalanges are fairly well developed, the distal epiphyses of the second through the fifth metacarpals and the proximal epiphysis of the first metacarpal are likewise well developed. There are well-developed centers of ossification for the capitate and hamate and beginning development of the center of ossification for the triangular bone.

Fig. 2.—View of the perineum showing enlarged labia, redundancy of the hymen, and enlargement of the clitoris.

There is a fairly good development of the distal epiphysis of the radius, but the distal epiphysis of the ulna has not yet appeared. The estimated bone age, on the basis of this hand and wrist, lies at approximately 3½ years.

"Within the hip regions the epiphyses for the greater trochanters of the femora have not yet appeared which means that here, too, the bone age has not as yet reached the 4-year period. Thus, the estimated bone age for this child on the basis of the films of Feb. 24, 1948, lies between 3 and 4 years of age at approximately 3½."* The child on this date was actually 1 year, 22 days.

meter; white blood count 6.25 thousand per cubic millimeter. Differential: basophiles 0, eosinophiles 0, myelocytes 0, juveniles 0, stabs 3, polymorphonuclears 50, lymphocytes 41, and monocytes 6.

The 17-ketosteroids were determined according to the usual method on a twenty-four-hour specimen of urine, collected preoperatively, which revealed 0.05 mg. per twenty-four hours.

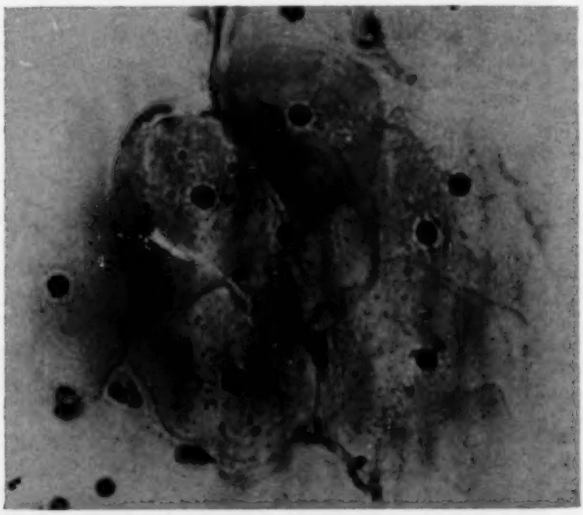

Fig. 3.—Photomicrograph of the preoperative vaginal smear, stained with hematoxylin and eosin showing the large cornified, squamous cells with shrunken nuclei.

Vaginal smears made preoperatively, and stained with hematoxylin and eosin, showed cornified epithelial cells comparable to those of women at the mid-interval of the menstrual cycle (Fig. 3). The vaginal discharge became bloody after a transfusion on Feb. 25, 1948, and remained so until the abdominal operation was done March 4, approximately a week later. The discharge was not profuse.

The blood examination preoperatively showed: hemoglobin, 47 per cent, 7 Gm. per 100 c.c.; red blood count 2.56 million per cubic millimeter; white blood count 6.25 thousand per cubic millimeter. Differential: basophiles 0, eosinophiles 0, myelocytes 0, juveniles 0, stabs 3, polymorphonuclears 50, lymphocytes 41, and monocytes 6.

The 17-ketosteroids were determined according to the usual method on a twenty-four-hour specimen of urine, collected preoperatively, which revealed 0.05 mg. per twenty-four hours. This result is at the lowest limit of excretion levels and is the figure expected for a child of this age.

An assay for urine gonadotrophins was carried out and none were found.

The twenty-four-hour specimen of urine was assayed for estrogen and found to contain the equivalent of 23 μg of estrone which is 230 I.U. This is well within the range of the normal adult-cycling female. (The daily excretion of estrogens in the first eight years of life is 0.10 I.U.[19]) No attempt was made to separate the various types of estrogen.

Technique of Urinary Assay for Estrogen.—A twenty-four-hour specimen of urine was hydrolyzed for two

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hours with concentrated hydrochloric acid (15 ml. concentrated acid for each 100 ml. of urine) over carbon tetrachloride (12 ml. per 100 ml. urine) in a reflux condenser. The carbon tetrachloride was removed with a separatory funnel and the urine extracted twice more in the separatory funnel with the same volume of carbon tetrachloride. The extracts were combined and the carbon tetrachloride was removed by vacuum distillation.

The residue was dissolved in 100 ml. of benzene and the solution placed in a separatory funnel, washed twice with 25 ml. portions of saturated sodium bicarbonate, and the washings discarded. The benzene solution was then washed five times with 20 ml. portions of 2N sodium hydroxide to remove the phenolic estrogens.

These washings were combined and neutralized with hydrochloric acid and the pH adjusted to about 5. This was then extracted with 25 ml. volumes of ether, five times. The extracts were each separated with a separatory funnel, combined and evaporated to a thick oil under reduced pressure. The residual oil was extracted with portions of ether and the extract made up to 100 ml. in a volumetric flask as a stock solution for assay.

Aliquots of the stock solution were taken for assay, dissolved in corn oil, and the ether evaporated from the oil. These oil solutions were used for assay, using the uterine weight of the 21-day-old rat as the test criterion. The results were compared with the effects of a known amount of crystalline estrone and the results expressed as international units equivalent. No attempt was made to separate the various types of estrogens.

Case Report (Cont'd).—A preoperative diagnosis of a feminizing tumor of the ovary, probably granulosa-cell type was made. The patient was seen in consultation with Dr. Henry Hollenberg, who concurred in this diagnosis and later performed the surgery with his assistant, Dr. Robert D. Jones.

Laparotomy was performed on March 4, 1948, when the child was 13 months of age. A tumor of the left ovary involving the entire organ was removed with the attached oviduct. It was smooth, attached by a long slender pedicle to the adnexa, and was not adherent to any other abdominal viscera. This would explain why the location of the tumor upon palpation was not always constant.

The left tube was somewhat enlarged and distally blended into the tumor mass.

The uterus was slightly enlarged.

The right ovary was smaller than normal and the right tube was enlarged. This is consistent with the endocrine findings to be discussed later. The left tube and ovary were removed.

Pathological Report of Tumor Removed.—

Gross Examination: The gross specimen consisted of the left fallopian tube and ovary. The tumor was 9 centimeters in diameter, solid, and completely encapsulated, and had a hard rubbery consistency. There was slight evidence of lobulation externally. The cut surface of the lobules protruded slightly above the level of the cut and were pale yellow in color (Plate I, *A*).

Microscopic Examination:

Ovarian Tumor: In sections of the tumor stained with hematoxylin and eosin, large cellular areas were seen, separated by fine strands of collagenous connective tissue (Plate I, *C*). The nuclei in the cellular areas varied from spherical to long, slender spheroids in shape. Nothing could be seen to indicate that any of these nuclei were flattened. In addition to the variation in shape, the nuclei definitely varied in size. The nuclei had well-defined membranes, had finely granular chromatin material, and usually only one karyosome although two and rarely three could be seen. In general, the nuclei were rather hypochromatic, and resembled the nuclei seen in the theca interna of the ovarian follicle. The cell limits were not sharply defined. Mitotic figures were quite rare in the section. The strands of connective tissue separating the cellular

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Plate I

A, Cut surface of the tumor showing the yellow color and the localized elevation of the lobules above the level of the cut.

B, Photomicrograph of a frozen section stained with hematoxylin and sudan IV, showing intracellular sudanophilic droplets surrounding the nuclei.

C, Photomicrograph of the ovarian tumor, stained with hematoxylin and eosin, showing the spherical and spheroidal nuclei, and the small strands of connective tissue. The spindle-shapedl fibroblastic nuclei, which appear hyperchromatic, and the hypochromatic theca-cell nuclei can be seen.

D, Photomicrograph of a frozen section stained with the de Galantha's silver stain showing large reticular fibers which branch into finer radicles surrounding individual cells.

areas appeared to be fibroelastic in nature and the delicate fibers were stained intensely with eosin. Arranged among the fibers were slender, elongated, sharply pointed nuclei of the fibroblastic (fibrocytic) type.

Formalin-fixed frozen sections stained with hematoxylin and sudan IV had sudanophilic droplets varying in diameter from less than 0.8 μ to 5 μ (Plate I, *B*). These droplets were apparently intracellular, and for the most part were located immediately surrounding the nucleus. Similar sections examined with the polarizing microscope contained birefringent granules which corresponded in location to, but were smaller in size and fewer in number than, the sudanophilic droplets. Sections treated with acetone had neither sudanophilic droplets nor birefringent granules.

Formalin-fixed frozen sections stained with silver for reticular material, according to the method of de Galantha,[20] contained an abundance of these fibers (Plate I, *D*). The larger fibers branched into finer radicles in intimate relation to individual cells.

Oviduct: Sections of the oviduct were unusual in that the organ was excessively developed for a child of this patient's age. The epithelium consisted of ciliated columnar cells 25 to 40 μ in height (Fig. 4). The nuclei were elongated and were located at different levels in the epithelium. The ciliated border was as complete as if every cell were ciliated. Beneath the cilia the surfaces of the cells stained deeply, suggesting that the surfaces were modified as terminal bars. The fact that fixation was started within five minutes after ligation of the blood vessels accounted for the fine cellular detail of this tissue. Except for mere gross size, this section corresponded in all details with sections of oviducts removed from women at about the time of ovulation.

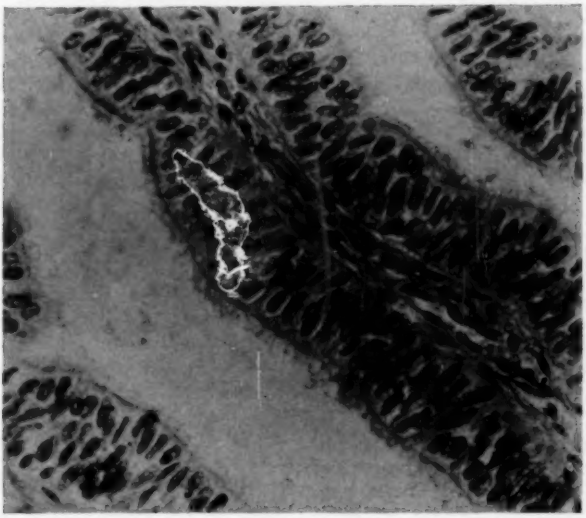

Fig. 4.—Photomicrograph of the mucosa of the oviduct, stained with hematoxylin and eosin showing the ciliated, columnar cells of the epithelium simulating that of an adult, ovulating female.

Tumor Assay.—The extract of the tumor was assayed and found to contain the equivalent of 2 I.U. of estrogen per gram of fresh tissue. This was calculated from the results of assays on larger amounts of tissue amounting to more than one single gram.

This low content of estrogen might be surprising but a review of the literature indicates that tumor tissue itself may be quite low in estrogens despite a high urinary excretion. This is explained on the basis that the tumor is excreting the hormone as rapidly as it is formed in the tissues. The amount of the fat-staining material in the tumor tissue would substantiate this concept.

In view of the importance of the diagnosis of this tumor in a child so young, it seemed advisable to submit sample sections to various pathologists. Their opinions were as follows:

Dr. Howard Karsner[21]: "This distribution of reticulin together with the lipid in the cells makes it seem reasonably certain to me that this tumor should be classified as a thecoma. . . It is not possible to classify this lesion as a granulosa-cell tumor."

Dr. Emil Novak[22]: "I would interpret the tumor as a typical thecoma. As in most such tumors, there are scattered among the thecomatous elements a good many cells of granulosa or granuloid appearance."

Dr. Joe Meigs[23]: "I looked at the tumor as it was given to me, one section of it, and it looked to me as though it were a theca-cell tumor, but I believe that theca-cell tumors and most granulosa-cell tumors are a combination of both. This one certainly has the thecal cell predominating."

Dr. Arthur P. Stout[24]: "In my opinion the tumor removed from baby--------- is a theca-cell tumor."

Dr. George T. Pack[25]: "We reviewed this tumor with our pathologist and we all agree that it is a thecal-cell tumor."

Postoperative Course and Present Status of Patient.—The child from whom the thecoma was removed is currently under well-child supervision by one of us (V. H. G.), and was examined at the age of 2 years, 7 months. She appeared to be in every respect a normal, healthy female of the stated chronological age.

Eye ground examination was entirely negative though she did show some evidence of alternating strabismus. Her breasts were average for a child of the stated age. Pubic hair had entirely disappeared. The clitoris and labia minora were no longer enlarged.

X-ray examination of both wrists, both hands, and both elbows one year, four months after surgery showed the following changes: "At this time there is further development of the proximal epiphyses of the phalanges and the epiphyses of the metacarpals. There is further growth and development of the centers of ossification for the capitate and hamate carpal bones as well as the triangular bone. There is the new appearance in the right wrist of the center of ossification for the lunate carpal bone and in the left wrist for the greater multangular carpal bone as well. In the case of the elbow, one can just barely make out a center of ossification for the proximal epiphysis of the head of the radius, and the epiphyses of the inner epicondyle of the distal humerus as well as the capitulum are well developed. It would appear that the proximal epiphysis for the head of the radius of the left elbow is somewhat further along in its ossification than that for the right.

"Conclusions: The estimated bone age on the basis of the survey made one year, four months after surgery is approximately 5 years of age. It would appear that the right elbow and wrist are not quite as advanced as those of the left side. Thus, it can be stated that the approximate degree of development of this patient's wrists and elbows is approximately equivalent to the chronological time interval between these two film survey studies, when one considers the left side particularly. The right side, however, is slightly delayed in comparison to the left."*

The given chronological age of the infant at this time was approximately 2 years, 9 months.

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A late postoperative vaginal smear taken three months after surgery showed that the vaginal epithelium had regressed and had become that of a normal female child (Fig. 5). She showed no evidence of anemia. Dentition was normal. She had sixteen teeth (3/8) at 2 years, 3 months.

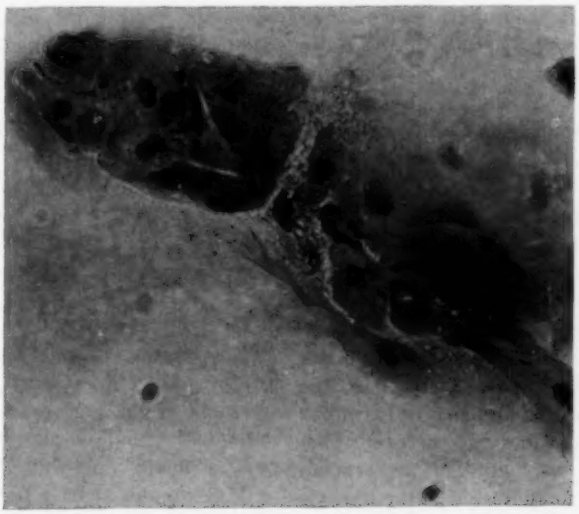

Fig. 5.—Photomicrograph of the postoperative vaginal smear stained with hematoxylin and eosin, showing the large vesicular nuclei of small, rounded, epithelial cells characteristic of a young child.

It might be of interest to state that the mother of the child discussed in this paper had a third female infant approximately two years after the birth of this child. The infant weighed 7 pounds, 3 ounces. The labor was short and uncomplicated and the condition of the baby for the first few hours was good according to the history.

One of us (V. H. G.) examined this baby less than twenty-four hours after birth and at that time there were no apparent abnormalities. The nurse did state that the infant had had several minor cyanotic attacks a few hours previously. When examined, the skin was pink, the cry was lusty, and there were no cardiac murmurs.

Forty-eight hours after birth, however, this infant developed petechiae all over the face and marked cyanosis with slight enlargement of the liver and spleen which had not been present when first examined. X-ray and fluoroscopic examination at that time revealed an enlarged heart.

The child died on the third day and autopsy revealed a moderate atelectasis of the lungs, and an enlarged liver and spleen. The heart showed complete absence of the right auricle with constriction of the pulmonary artery and poorly formed valves. There was also incomplete formation of the interventricular septum and a patent foramen ovale.

DISCUSSION

This case report of a theca-cell tumor of the ovary producing feminizing characteristics in an infant logically provokes an academic discussion of the significance of such tumors.

A natural consequence of the isolation and identification of estrogenic materials in 1924[26] has been the re-

peated attempts to determine the ovarian tissue or tissues which produce them. Although relatively neglected by those engaged in clinical investigation, this problem has been actively studied by others.

Mossman and his group have reported that in the guinea pig[27] and the pocket gopher[28] the cells of the theca interna reached maximal development at a time "when the greatest amount of follicular hormone has been demonstrated to be present." The same conclusion has been drawn from studies on many other species, and recently McKay and Robinson[29] showed that the human ovary conforms to the general pattern. According to their work, "birefringent granules first appear in follicles at the time of antrum formation, and are *never* seen in the granulosa cell layer prior to luteinization." Their findings were corroborated when they studied the ovarian tissue for autofluorescence, the phenylhydrazine reaction, and chromogenic properties with sulfuric acid. The physical and chemical properties of sterol estrogens are such that, with the findings mentioned above, McKay and Robinson feel it is safe to conclude that the cells of the theca interna are the follicular source of estrogens.

It seems reasonable to assume that this function is carried forward after luteinization, and that the theca lutein cells produce the estrogen during that phase of the cycle. Perhaps the role of progesterone production can be assigned to the granulosa lutein cells since it is only during the luteal phase of the cycle that one sees histochemical signs of activity in the lutein cells of granulosa-cell origin. In support of the duality of cell origin of the corpus luteum in the human being, the reader is referred to the work of Corner.[30]

In view of these statements it would appear advisable to re-evaluate the relationship, whether causal or casual, between the cellular composition of ovarian tumors and the presence or absence of feminizing influences. Tumors often create unusual endocrine situations, and from these "natural experiments" interesting information frequently can be derived. Although such information may be of no consequence in determining the treatment, it is very valuable to the fundamentalist in understanding the basic physiological principles in operation.

SUMMARY

The literature on theca-cell tumors of the ovary is reviewed. A case of thecoma of the left ovary in a 1-year, 8-day-old female is described. There was a history of white vaginal discharge present shortly before one year of age, and, subsequently, vaginal bleeding occurred. Examination revealed a slightly enlarged uterus in the lower abdomen, an approximately 3×3 cm., freely movable, smooth, hard and nontender tumor mass. Breasts were enlarged to about the size of those of a 12-year-old girl, and pubic hair was present. The labia minora were definitely enlarged and there was redundancy of the hymen.

The 17-ketosteroid determination revealed 0.05 mg. per twenty-four hours. The urine collected over a twenty-four-hour period contained the equivalent of 230 I.U. of estrone, an amount well within the range of the normal, adult, cycling female.

The tumor tissue was assayed for estrogen and found to contain the

equivalent of 2 I.U. per gram of fresh tissue.

Preoperative vaginal smears revealed cornified epithelial cells comparable to those of women at the midinterval of the menstrual cycle. Late postoperative vaginal smears showed regression of the vaginal epithelium to the infantile condition.

The diagnosis of theca-cell tumor in this case rests on the presence of intracellular and extracellular lipoid droplets containing birefringent granules, and large amounts of reticular fibrils.

This is one case which supports the view that an ovarian tumor can produce feminizing characteristics, and contain by far a major portion of theca-cell rather than granulosa-cell element.

The authors wish to express appreciation for the assistance of the following: Schering Corporation, Bloomfield, N. J., for estrone used as standard, and for financial support of reproduction of the color plate; Wynne Eastman Medical Photographic Laboratory, 1705 Crawford, Houston, Texas, for the photomicrographs; and Dr. Robert D. Jones, Little Rock, Ark., for color pictures of the tumor and the photograph of the baby.

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THE TREATMENT OF ACUTE POLIOMYELITIS

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BECAUSE of the limitation of time, this talk will consist, not of discussion, but of a series of statements, occasionally disconnected, but believed to be factual. Some might be considered polio aphorisms.

To a patient just coming down with polio, a long trip to a hospital may be harmful. Hospitalization of each and every case is not necessarily essential. For control of polio contagion, hospitalization is ineffective and unwarranted. Given favorable home circumstances, polio suspects, nonparalytic cases, and even minor paralytics can be diagnosed and cared for at home to the patient's distinct advantage.

Physical exhaustion the last day or two of the incubation period and the first day or two of the fever may seriously aggravate the oncoming illness. Thus, in the acute stage of polio, the patient's comfort and peace are more important than positioning. A maximum of rest and a minimum number of examinations are essential in early care.

So, patients with fever, but in natural sleep, should not be awakened for anything. Sedation by medication may be dangerous lest there be breathing difficulty. A patient with breathing difficulty but kept by sedation from the voluntary effort necessary for maintaining respiration may cease breathing in his sleep.

Reading aloud to the wakeful, restless patient is good treatment for an early case. It keeps the mother busy and the patient quiet. His bed should be firm and level, and not sagging.

The spinal fluid findings do not "confirm the diagnosis" but may be "consistent with the diagnosis of polio."

MUSCLE PAIN AND SPASM

For tightness and pain in the muscles, the treatment that is most widely accepted is moist heat—best applied by hot tubs, especially in private homes. Also, often by a slight change of position and a gentle movement of the patient's joints, a nurse can bring comfort—especially with the help of a baby pillow here and there.

If hot packs are used, it is important to have the skin dry out between packs. Continuous moist heat may lead to vasomotor failure, while alternating mild hot and cold has a vasomotor tonic effect.

Since in early cases most of the tight muscles are posterior—that is neck, back, and hamstrings—laid-on packs with the patient prone are adequate, and disturb the patient less than wrap-around packs. Known as prone packs, they are renewed in ten minutes for an additional ten-minute period, and the patient is packed three such sessions daily, with a standing repeat order in case of discomfort at night.

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Muscle temperature studies have proved such packs most effective. Unless the patient is sleeping, they may well be followed with gentle passive motion, but always short of pain and fatigue.

Quinine is commonly effective when given for the treatment of the cramps and muscle twitchings that occur during acute polio.

INTRAVENOUS FLUIDS

At autopsy the weight of the brain of the polio patient is always above normal—presumably due to interstitial edema which may interfere with capillary circulation and thereby with the oxygen supply of affected neurones. Some experienced clinicians believe the intravenous administration of moderate amounts of 10 per cent glucose is often beneficial, that is, a liter for an adult, children in proportion by weight, given early and slowly, and usually only once. The effect may not be one of dehydration, but may be because glucose is protective of oxygenation of neurones.

On the other hand, flooding a patient intravenously (too much and too fast) affects the heart, increases pharyngeal secretion, and may tend to precipitate pulmonary edema. Kubicek states that the lung when hypoxic is very sensitive to excess water in the blood stream. Infusions in polio should be 100 to 200 c.c. per hour and the specific gravity of the urine kept between 1.025 and 1.030.

Some patients when first seen are already dehydrated by vomiting or by a recent low intake of fluids. Moderate amounts of 5 or 10 per cent glucose intravenously may be dramatically beneficial.

If the blood pressure is appreciably elevated, intravenous fluids should be given only with caution. Fluids, especially glucose solution, when given subcutaneously or intramuscularly, aggravate the muscle tightness and soreness which are part of poliomyelitis.

Patients who are dehydrated should not be made to perspire as by hot packs.

BREATHING DIFFICULTIES

The causes of breathing difficulty in polio are complex and should be thoroughly studied in each case and clearly differentiated. The treatment will vary markedly according to the causes. In some cases the breathing mechanism is at fault; in others, there is interference in various ways with oxygen and carbon dioxide exchange; and there may be several contributory factors, such as panic, anemia, and abdominal distention.

For the proper management of patients with bulbar and breathing difficulties, teamwork is essential. In particular, the help of laryngologists, anesthetists, and biochemists may be invaluable.

There are two factors that are essential for normal respiratory gas exchange: first, the inspiration of oxygen of sufficient pressure and quantity to saturate the arterial blood; and, second, ventilation that is adequate to wash out enough carbon dioxide to prevent the development of respiratory acidosis.

The respiratory difficulty that results from interference with oxygen and carbon dioxide exchange by secretions accumulating in the upper respiratory tract naturally requires the removal of these secretions by postural drainage and aspiration. Hospital teams vary as to their ability to accomplish this. Until these secretions are removed, artificial respiration is dangerous.

Artificial respiration for polio patients may be accomplished by a number of methods:

First, by extrathoracic positive pressure—manually, or in a tank respirator suitably adjusted.

Second, by extrathoracic negative pressure, as in the usual use of a tank respirator or of a chest respirator.

Third, by positive pressure on the upper respiratory tract, applied rhythmically by a face mask or a hood, or by special apparatus to a tracheotomy tube—the so-called Intermittent Positive Pressure Breathing, or I.P.P.B.

Fourth, by action on the diaphragm, either by a rocking bed or a seesaw, or by electric stimulation of the phrenic nerve.

These methods vary materially in their respective effects on oxygenation, elimination of carbon dioxide, cardiac action, and intrathoracic circulation, also on blood pressure. Some of these effects are not yet clearly understood, especially as regards circulation. But it has been demonstrated that extrathoracic negative pressure and upper respiratory positive pressure, by causing the same pressure gradient changes in the thorax, have the same effect on venous pressure, on the filling of the heart, on the lung capillary field, and on pulmonary edema—at least in dogs and in the inert human being. However, the tight chests and diaphragms of polio patients may be an altering factor. One must remember that the pressure gauges of many tank respirators register too high.

Upper respiratory, positive pressure breathing can lower the cardiac output presumably by the effect on cardiac filling. It promotes bronchial drainage, effects more uniform alveolar aeration, protects against atelectasis, increases the lymph flow from the lungs, and in particular it can be used to combat pulmonary edema. It helps to establish normal carbon-dioxide elimination.

In normal respiration the upper respiratory pressure of 2 to 3 mm. Hg alternates from positive on inspiration to negative on expiration. For intermittent positive pressure treatment, 3 to 4 mm. Hg during inspiration is desirable. This is roughly equivalent to 4.5 to 6 cm. of water pressure.

For the best treatment of respiratory difficulties, one must be able to evaluate possible carbon-dioxide retention and the resulting respiratory acidosis.

Respiratory acidosis due to the retention of carbon dioxide may cause delirium, coma, convulsions, and death. It can best be detected by evaluation of the carbon-dioxide content of the alveolar air which has an average of 40 mm. of pressure. Climbing of the carbon-dioxide combining power of the venous blood plasma above a normal of 62 volumes per cent or a dropping of the urinary pH are also useful laboratory determinations for respiratory acidosis that are perhaps more readily accomplished. Elevation of blood chlorides above a normal of 550 mg. may also be found in respiratory acidosis.

Feeding oxygen steadily to a patient by passing it through a catheter inserted in a tracheotomy tube in situ is almost certain to cause carbon-dioxide retention and respiratory acidosis.

According to Motley: Since the use for respiratory stimulation of carbon dioxide with oxygen only increases the acidosis of the patient in need of artificial respiration, there is no rationale for such use. The blood carbon-dioxide level is already above normal, so that the carbon dioxide no longer acts as a

respiratory stimulant but in fact may be a depressant.

When carbon dioxide has been retained and there is respiratory acidosis, the excess carbon dioxide should be "blown off" by forced respirations with temporary overventilation.

Encephalitis in polio may cause symptoms similar to those of hypoxia and therefore should be treated with oxygen and perhaps at times even with artificial respiration.

It is better that the collar of a tank respirator leak a little around the patient's neck rather than be tight and obstruct venous drainage from the head.

Artificial respiration by means of a rapidly rocking bed is indicated for mild cases of respiratory difficulty and for weaning patients from tank respirators. When a rocking bed is used continuously for days for patients with marked intercostal and diaphragmatic weakness, there may be inadequate removal of carbon dioxide and resulting respiratory acidosis. This fact applies also to chest respirators.

The contraindications to the use of a rocking bed for artificial respiration are: (1) bulbar cases with diminished ability to swallow; (2) severe breathing difficulty with minimum chest excursion; (3) diaphragms handicapped because too tight, or by a distended stomach or a distended bowel.

When in bulbar cases there is evidence of weakness of the respiratory center and if a phrenic nerve to the diaphragm is healthy, Sarnoff's method of artificial respiration by rhythmic electro-phrenic stimulation may be lifesaving. This may also be useful for encephalitic cases, some of whom seem to forget to breathe when they are sleeping.

Watching the vital capacity of a patient having artificial respiration is of value in the process of weaning from the respirator. A decreasing capacity indicates a degree of fatigue which should be prevented while observance of an increasing vital capacity permits more constant progression.

Respirator cases tend to develop changes in bone, muscle, fascia, joint, and periarticular structures, despite the highest type of care. Muscles and fascia may shorten if not occasionally stretched. Occasional forced deep breaths are indicated for all patients with tight chests, as are also daily short periods of hyperextension of the spine.

The prime indication for tracheotomy in polio is obstruction to the air passageway resulting from bilateral abductor paralysis of the vocal cords.

Tracheotomy may also be indicated if the upper respiratory passageways cannot otherwise be kept clear, or when there is evidence of increasing hypoxia, not otherwise correctible.

Polio teams, and hospital staffs in general, vary markedly in their ability to give patients adequate care without resorting to tracheotomy. For some patients, however, the operation may truly be lifesaving.

Atelectasis is a common complication of patients with breathing difficulty, especially those that cannot cough. It is evidenced by an increasing dyspnea, and pulse rate, and by a dislocation of the heart apex to the affected side. Massive atelectasis should be treated by immediate bronchoscopy and suction.

Repeated periods of intermittent positive pressure breathing applied to the upper airway appear to offer effective prophylaxis against the development of atelectasis.

A patient lying on his back whose tongue has bilateral weakness may have a choking sensation from the tongue's falling back into his throat. Such a patient should be kept on his side.

DIFFICULTY IN SWALLOWING

Bulbar patients with inability to swallow are usually given postural drainage by being put in the side resting position with the foot of the bed moderately elevated. To lessen possible cerebral congestion their beds may be put flat for several short periods a day, but during such periods they may require even more constant nursing care, such as pharyngeal suction. If several such patients are in the care of one nurse, only one should be put flat at a time.

After a bulbar patient's temperature has been normal for forty-eight hours, if there is no further nausea and if the patient is complaining of thirst and seems able to swallow his own saliva, very small amounts of water may be offered by teaspoon at half-hour intervals, increasing gradually. Milk is not well tolerated the first several days of returning swallowing. Fluids should not be left by the unattended bedside of such patients, if only because fatigue causes further difficulty in swallowing.

A bulbar patient whose inability to swallow is clearing up and who has begun again to eat should not be allowed to eat unattended lest he choke on some food and need immediate help, such as to be turned over, head down, and patted on the back to bring up the food.

THE USE OF ANTIBIOTICS

For a patient with polio, the indications for antibiotics are: (1) respiratory difficulty with its danger of pneumonia; (2) catheterization with its danger of secondary infection; (3) an appreciably elevated leucocyte count, suggesting a secondary bacterial infection.

Finally, the art of skillful patient care is often vital to the patient's survival and welfare. To quote Whittenberger: "Good records in polio treatment depend more on alert, intelligent medical practice and nursing care than on minor variations in equipment."

DISCUSSION BY DR. HORACE L. HODES OF NEW YORK

Dr. Stimson has outlined in a very able and concise way many of the important problems presented by the patient with poliomyelitis. As he has indicated, the chance of survival of the individual suffering a severe attack of poliomyelitis depends to a very large extent upon the accurate appraisal of complex alterations in the functioning of a number of vital physiologic mechanisms. During the past few years the studies of physicians trained in physiology and neurophysiology have led to a much clearer understanding and more rational treatment of some of these changes. There remain, however, a number of unsolved problems which appear worthy of experimental study. One of the most important of these revolves around the question of possible changes in water content of the body as a whole and of the central nervous system in particular during the course of poliomyelitis. It is believed by many that edema of the brain and spinal cord occurs regularly in poliomyelitis and that this edema may cause secondary injury to neurones damaged by the virus. Because of this belief a number of clinicans with wide experience in the treatment of poliomyelitis consider that attempts to reduce this edema are warranted. For this purpose hypertonic glucose solutions have frequently been employed, and beneficial results following their

use have been reported. That the use of hypertonic solutions has sometimes been followed by improvement in the patient's condition cannot be doubted. It is possible, however, that this improvement may be due to some effect other than the dehydrating effect of hypertonic glucose solution. It is known that the injection of hypertonic glucose is followed by a decrease in the volume of the brain, but that this effect is temporary and is followed by a "rebound" to the original state. No deleterious rebound effect following the use of hypertonic glucose solutions in poliomyelitis has been described.

The question of alteration in the water content of the central nervous system in poliomyelitis seems susceptible of solution by experimental methods. It has recently been shown that infection of mice with MM encephalitis virus causes a significant increase in the water and sodium content of the brain as compared with normal controls. We are about to undertake experiments to determine whether similar changes occur in primates infected with poliomyelitis virus. The outcome of these experiments may serve as a starting point for a rational consideration of the effect of hypertonic solutions in the treatment of poliomyelitis in human beings.

My personal experience with poliomyelitis inclines me to the belief that children with severe poliomyelitis are more likely to be in need of isotonic solutions of glucose and electrolytes rather than hypertonic ones. This is particularly true of patients with bulbar involvement who are unable to take food or fluids and in addition lose water and electrolytes through expectoration of saliva which they are unable to swallow. Such children show clinical and laboratory evidence of dehydration which is sometimes of severe degree. It seems difficult to believe that restoration of water and electrolyte content of plasma extracellular fluid, and perhaps of the cells, is not of prime importance for the survival of such patients.

Dr. Stimson has touched upon the problems which arise as the result of weakness of the muscles involved in the swallowing mechanism. Difficulty in swallowing arises from loss of function of the neurones of the nuclei of the ninth, tenth, and eleventh cranial nerves. Saliva and mucus may accumulate in the region of the epiglottis and interfere with the entrance of air into the larynx and trachea. In addition, with attempts at inspiration the pooled material may be aspirated into larynx, trachea, and bronchi causing sudden asphyxia.

To avoid these dangerous possibilities, attempts to keep mouth and pharynx free of fluid are made. The foot of the bed is elevated. A catheter is passed through the nose into the back of the pharynx and allowed to remain in position for several days at a time. The catheter is connected to an electrically driven suction machine which is allowed to run almost constantly. In addition, a nurse remains in attendance, ready to use an auxiliary suction apparatus consisting of a curved metal tube which is readily passed through the mouth into the pharynx. If such measures fail, a tracheotomy is performed under local anesthesia thus providing an airway which is free from danger of being occluded by the fluid accumulating in the pharynx. Another advantage gained by tracheotomy is that any fluid which is aspirated into the trachea is readily removed by suction through a soft rubber catheter passed through the tracheotomy tube.

I believe that nearly all physicians who have had extensive experience in the treatment of poliomyelitis believe that tracheotomy is indicated under certain conditions. There is some difference of opinion regarding these indications, although these differences on investigation are not so great as appears to be the case at first sight. On many occasions in our experience, tracheotomy has been a lifesaving measure but we do not mean to imply that all poliomyelitis patients who present evidence of difficulty in swal-

lowing should be subjected to tracheotomy. The individual situation is carefully weighed, and tracheotomy is done only if we do not feel reasonably certain that we shall be able to keep the airway unobstructed by other means. In general, the cooperative patient is less likely to need tracheotomy than one who is panic stricken and unmanageable. Adults and older children require tracheotomy much less often than very young children, and infants. A patient with weakness of the muscles of deglutition who is able to be maintained safely by aspiration of the pharynx may require tracheotomy if he becomes exhausted or comatose.

A patient with paralysis of the muscles of deglutition may also have paralysis of the intercostal muscles and diaphragm sufficient to require treatment in the respirator. In this situation, the danger of aspiration is extremely great. Presumably, this is due to the fact that the respiratory movements, in the respirator, are beyond the control of the patient and inspiration may occur at the very moment that secretions have accumulated over the epiglottis, causing fluid to be sucked into larynx and trachea. When this occurs, sudden death may follow. For this reason, we usually perform a tracheotomy on patients with severe weakness of the muscles of deglutition if it becomes necessary to place them in a respirator. In this way the danger of fatal aspiration of secretions into the respiratory tract is minimized.

Finally, it should be stated that in a general way the attendance of nurses and physicians with great skill and wide experience in the treatment of patients with bulbar poliomyelitis may eliminate the need for tracheotomy when under less favorable circumstance performance of this operation would be imperative.

TERRAMYCIN THERAPY FOR MENINGITIS

A Report of Fourteen Recoveries Without Other Medication

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THERE has been continued progress in the treatment of meningitis for many years.[1] Before the advent of the sulfonamides, when antisera were used, the general fatality rates for meningococcic infections were seldom less than 50 per cent and often much higher. Other forms of meningitis were usually 100 per cent fatal. Nevertheless in those earlier days one[2] of us obtained recovery rates for meningococcic infections comparable to the present. That was accomplished with the administration of antiserum exclusively by the intravenous route.

Now almost any one of the better known sulfonamides is capable of promoting recovery in most cases of meningococcic meningitis. Moreover there seems to be little doubt that the same drugs are beneficial in the majority of other bacterial infections. However the sulfonamides have some disadvantages, especially in respect to renal irritation, causing in rare instances even blockage of ureters. Penicillin, although of great value in pneumococcic meningitis and helpful in some other forms, cannot be accepted as a general substitute for the sulfonamides in the therapy of the meningidities.

In recent years several antibiotic agents have been produced and their effectiveness tested in combating different kinds of meningitis. Regardless of any efficiency determined in the treatment of some specific disease, each one of these agents has generally disclosed some disadvantage. Because of toxicity, streptomycin[3] may cause impairment or even loss of hearing. A similar sequelae may result with dihydrostreptomycin although it is less toxic. Some of the other antibiotics in general use may be responsible for nausea, vomiting, or diarrhea. Certain antibiotics cannot be given intravenously and others should not be injected in the muscle because they are too irritating. From the standpoint of administration, penicillin is the only one that is ideal because it may be prescribed by any route. However, it is our[4] opinion that no remedy should be introduced into the thecal sac.

On account of some of the foregoing reasons, we decided to make a clinical investigation of the value of terramycin in the therapy of meningitis. In the beginning our plan was to select the first mild-appearing meningococcic meningitis patient admitted to hospital and start treatment with terramycin exclusively. If there was not a satisfactory response within twenty-four hours, we proposed to institute our customary sulfonamide program.

Our first patient admitted March 13, 1951, was a 3-year-old male. A smear from petechiae revealed extracellular and intracellular gram-negative diplococci. Although there was marked rigidity of neck and Kernig and Brudzinski signs were positive, no lumbar puncture was made. We felt that the clinical diagnosis was con-

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The terramycin used in this investigation was supplied through the courtesy of Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

firmed by the presence of meningococci in the skin. The temperature was 103° F. rectally. Two hundred fifty milligrams of terramycin in 100 c.c. of physiologic salt solution were started at once by the drip method intravenously. In addition, 166 mg. in 50 c.c. saline for intravenous administration were prescribed every four hours until discontinued on the sixth day. This is the only patient in our series who received all the terramycin by vein. At the beginning of the third hospital day the rectal temperature was 99° F., the nuchal rigidity had subsided, and the patient's condition was good. However, he resisted oral medication. Hospital dismissal was March 23, ten days after entry.

Between March 15 and May 15, 1951, thirteen consecutive additional meningococcic patients were treated with terramycin. The ages ranged from one to 36 years. Age, sex, presence or absence of petechiae, and other data are set forth in Table I.

TABLE I. ANALYSIS OF PATIENTS

CASE	AGE	SEX		PETECHIAE	LUMBAR PUNCTURE
		M	F		
1	3	x		x	0
2	18		x	x	1
3	4		x	x	0
4	1		x	0	1
5	5	x		x	0
6	4	x		x	0
7	36	x		0	1
8	3		x	x	0
9	25		x	0	1
10	2		x	x	1
11	2	x		0	1
12	2		x	x	0
13	15		x	x	0
14	2	x		x	1
Total		6	8	10	7

It may be noted that ten of the fourteen patients had petechiae and that only three of those ten had lumbar punctures. Cerebrospinal fluid was examined only when a petechial smear was negative or questionable or in those cases which had no petechiae. The clinical diagnosis was confirmed in every instance by laboratory procedures. Positive blood cultures were reported in four cases and in two others cultures of spinal fluid were positive. An additional patient had positive cultures for meningococci from both blood and spinal fluid. Gram-negative smears for meningococci were identified in all cases in which spinal fluid was examined.

Each patient was given the initial dose of terramycin intravenously. We were aware of the possibility of thrombosis when selecting this route but felt it was indicated. Among the first four patients, three developed some thrombosis in the leg about the site of injection. Thereafter we increased the dilution to 1 c.c. for each milligram of the drug, using 5 per cent dextrose for the solution. Only one additional case of thrombosis occurred. For children, our initial intravenous dose was 250 mg. of terramycin and in some instances this was repeated. However, we believe it best to discontinue this route as soon as possible and resort to oral administration. Our oral dose varied from 250 mg. for children to 500 mg. in older patients at from four- to six-hour intervals, the latter spacing probably being satisfactory in most cases.

Terramycin should not be administered orally on an empty stomach. We found that no gastric distress occurred if the drug was given after eating or if a glass of milk was taken with the medication. Before adopting the latter precaution a few instances of nausea were noted. In three cases there was a slight diarrhea which was probably due to the drug.

In Table II there is indicated the number of days meningeal signs persisted which includes any evidence of stiffness of neck; the number of days treatment, total dosage, and hospital days are also listed. Patients were not released until they had maintained a normal temperature for at least three consecutive twenty-four-hour periods following discontinuance of terramycin.

ter the cerebrospinal fluid when prescribed orally has detered some investigators from using this new antibiotic in cases of meningitis.

It is regretted exceedingly that it was not possible to secure blood and cerebrospinal fluid levels at the time our patients were under observation. We recognize fully that such procedures are of scientific interest and may be of value in estimating mini-

TABLE II. TERRAMYCIN THERAPY

CASE	DOSES I.V.	ORAL TREATMENT FOLLOWED IN HOURS	MENINGEAL SIGNS ABSENT (DAY)	THERAPY DISCONTINUED (DAY)	TOTAL DOSAGE (GM.)	HOSPITAL (DAYS)
1	26		5	6	4.02	11
2	14	60	11	11	10.25	15
3	6	28	4	8	12	12
4	3	26	4	8	5.5	11
5	1	6	4	8	11	11
6	5	36	6	7	7.5	11
7	1	6	7	7	12	11
8	1	6	3	7	9.5	10
9	1	6	5	6	7.75	8
10	3	26	6	8	6.5	14
11	1	6	5	7	5	9
12	4	30	4	7	5	10
13	1	6	8	9	14.5	12
14	1	6	7	7	9.25	13
Average	4.8	26	5.8	7.6	8.55	11.3

In addition to the cases of thrombosis mentioned, there was one instance of arthritis involving the right elbow without suppuration. There were no other complications and recovery was complete in every patient. There was a follow-up at intervals of from two to four weeks and all patients were found to be in good condition both mentally and physically.

In so far as we have been able to ascertain this is the first report of any series of patients with meningitis to be successfully treated with terramycin. Possibly the announcement by Herrell, Heilman, Wellman, and Bartholomew[5] of the Mayo Clinic that terramycin does not readily enmal and maximal dosage. Nevertheless too much thought should not be directed to cerebrospinal fluid levels as has been pointed out by one of the writers.[6]

Four influenzal meningitis patients were also treated with terramycin. The ages were 6 months, 9 months, 4 years, and 6 years. In these cases, however, sulfadiazine was used as well as terramycin. Nevertheless, we were convinced that terramycin was an important factor in bringing about recovery in three of the patients. The fourth was a 4-year-old boy who entered hospital in a desperate condition and died six hours later.

At the present time we are treating a 40-year-old man who has pneumo-

coccic meningitis. He is receiving terramycin exclusively. His diagnostic lumbar puncture revealed "too many cells to count" in the spinal fluid. No additional punctures are anticipated and his recovery is expected.

The number of days of medication with terramycin has averaged about three less than has been usual with sulfonamides. Moreover, the average hospital stay has been shortened more than two days.

SUMMARY

Fourteen consecutive patients with meningococcic meningitis were treated with terramycin exclusively. The ages ranged from 1 to 36 years. There were no deaths.

Seven of the patients had no lumbar punctures but the diagnosis was proved in all fourteen by laboratory procedures. Seven patients each had one spinal tap.

Every patient received the initial dose of terramycin intravenously. With a dilution of 1 c.c. of 5 per cent dextrose to each milligram of terramycin, thrombosis occurred but once among ten patients.

The average number of days of treatment was 7.6 and average total dosage of terramycin was 8.5 Gm. Although recovery often seemed to be complete within six days, the average hospital stay was 11.2.

There were practically no unpleasant reactions from the drug.

We believe these are the first meningitis patients treated exclusively with terramycin that have been reported.

In addition, three patients with influenzal meningitis were treated successfully with a combination of terramycin and sulfadiazine. One of these patients admitted in a comatose condition and with a temperature of 105° F. made a spectacular recovery in a week's time. One patient with pneucoccic meningitis is now being treated and he has shown an excellent response to terramycin without other medication.

COMMENT

Even on the basis of our limited experience with terramycin as a therapeutic agent for meningitis we believe this antibiotic may prove to be the ideal drug for combating meningococcic and influenzal infections. It is also possible that it may be effective in other forms of meningitis, including pneumococcic. Again we would like to emphasize that none of the patients mentioned had any intrathecal treatment, that seven had no lumbar punctures, and that the remainder including the influenzal cases and the one pneumococcic had but one puncture each.

Note: Since the preparation of this paper we have had nine additional patients treated exclusively with terramycin. Of that number, six had pneumococcic meningitis; five recovered and one died, the latter due to bilateral pneumonia. The three other patients each had *Hemophilus influenzae* meningitis and all recovered. Their ages were 4 months, 9 months, and 3 years.

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EVALUATION OF THE TREATMENT OF PRIMARY ATYPICAL PNEUMONIA WITH AUREOMYCIN, CHLOROMYCETIN, AND TERRAMYCIN

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PRIMARY atypical pneumonia has been the subject of many reports since 1948 when aureomycin was found to be effective in the treatment of this disease. The results with aureomycin have been good in most cases and it is now generally accepted as a therapeutic agent in this condition. Chloromycetin has been less used but has given favorable results thus far. Use of terramycin has been reported by Melcher and associates[1] in seven cases in adults with good results.

The number of cases of atypical pneumonia treated with aureomycin reported in children has been small but the results have been about the same as in adults. Olshaker and collaborators[2] reported a series of nine cases using aureomycin with good responses in eight cases. Anderson[3] treated nineteen patients with aureomycin having satisfactory results in all. Cohen and Schwartz[4] reported eleven patients treated with Chloromycetin. There were striking responses in ten of these.

It was felt that a comparative study of the effectiveness of the available antibiotics on a large series of pediatric patients would be of value.

Epidemiology.—In August, 1950, at the Army dependent housing center, Bad Mergentheim, Germany, the incidence of upper respiratory disease in young children was noted to be increasing rapidly. Although an occasional case of atypical pneumonia had been seen previously, one to four new cases were then being seen daily. A controlled study was set up to evaluate the relative merits of Chloromycetin, aureomycin, and terramycin.

Living conditions before and after arrival here deserve mention since there were many factors involved which made spread of the disease more diffuse. Families are sent here directly upon landing in Europe. Prior to leaving the United States they had usually been traveling for several weeks visiting relatives, and so forth. The ten-day trip to Europe was accomplished by ship with usually two adults and two children to a cabin. Meals were served in a common mess hall. During this period on shipboard the majority of the children had what were described by the parents as "common colds." On arrival here they were billeted in hotel rooms, usually two adults and two children to a room. Meals were served in a common dining room and most of the recreational activity was also of a group nature.

The anxiety of travel, the emotional upset of a disturbed routine (resulting in poor sleeping and eating habits), the close association with a large number of other children, and the family unit living in one room resulted in marked lowering of individual resist-

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Terramycin was supplied by Chas. Pfizer & Co., Inc.

ance and favored the spread of upper respiratory disease. Spread within the family unit occurred in almost all instances with an apparent incubation period of seven to ten days in infants exposed only to siblings.

Diagnosis.—There was a history of a nonproductive cough without notable coryza which was of increasing severity. The duration of the cough varied from one to twenty-one days previous to the development of fever. It was usually worse at night and parents frequently stated, "the children cough their heads off all night." This was associated with loss of appetite, irritability, and malaise. Temperature elevation was present in 108 patients for at least twenty-four hours before therapy was started.

Physical examination revealed abnormal pulmonary findings in 61 per cent of the patients on admission. The most common finding was "sticky" râles over the involved lung. Bronchial râles were present in 20 per cent of the patients. Increased respiratory rate was seen in 19 per cent of the patients, most of these under one year of age. An additional 23 per cent developed localized râles during their hospitalization. The remaining 16 per cent had no pulmonary findings on physical examination.

Definite x-ray evidence of pneumonia was present in all patients. The x-ray findings varied with the age of the patient but they had certain things in common. The earliest findings were usually those of increased hilar shadows and increased bronchial markings. The children from 3 to 5 years of age usually developed a lobular type of infiltration involving one or more lobes. The children from 9 months to 3 years of age usually showed a patchy peribronchial infiltration with more extensive general involvement. Those under 9 months of age usually developed a fine hazy ground-glass type of infiltration most commonly involving all lung fields with little normal aeration seen. No type was limited to any age group.

There was normal to low leucocyte count, except in five patients with superimposed infection (otitis media, two patients; streptococcal tonsillitis, three patients). There was a predominance of lymphocytes in 80 per cent of the patients.

Normal bacteria flora was found on nasopharyngeal culture. Pneumococci were found in six patients but were not typed since typing sera were not available.

Additional Criteria Used on a Limited Number of Cases.—

During the early part of the epidemic twelve patients were given penicillin for forty-eight hours to demonstrate that it gave no clinical or x-ray improvement. The temperature of one patient, who had a complicating otitis media, fell from 104.5° to 101° F. but no further improvement followed. Subsequent patients received no penicillin. One child was given penicillin prior to treatment with terramycin.

Serological studies on twenty patients done on admission and after three weeks were negative for influenza A and B and Q fever. Cold agglutinins done on admission were negative in thirty-three of the thirty-four patients. The other child had a titer of $\frac{1}{16}$ which rose to $\frac{1}{64}$ in three weeks. On the specimens drawn in three weeks there were twelve patients with titers of $\frac{1}{32}$ or over.

MG streptococcus titers were not

done because the laboratory was unable to isolate an organism.

Serological studies were limited since many patients left here before a three-week interval had elapsed.

Serological studies were done by the 4th Medical Laboratory, Heidelberg, Germany.

Study of Patients.—

1. On arrival here chest films were obtained on all children.

2. Admission to the hospital of all children who developed or had temperature in whom x-ray showed a pneumonia.

3. Admission of children who were moderately to serevely ill with positive x-ray findings and no fever.

4. On admission a repeat chest film, complete blood count, urinalysis, pharyngeal culture and first and second strength purified protein derivatives were done; blood was drawn for cold agglutinins, and influenza A and B and Q fever titers. Tuberculin tests were negative in all cases.

5. As soon as the diagnosis was established the patient was started on treatment. Alternate patients received aureomycin and Chloromycetin, respectively, during the first seven weeks. From the seventh to fourteenth week all patients under one year of age were given Chloromycetin. The remaining cases were alternated as before. Terramycin became available during the fourteenth week. After this, patients under one year of age were given terramycin and the rest of the patients rotated among the three drugs. Every twentieth patient was untreated as a control. No patients under one year of age were included as controls because of the increased severity in this age group. The change in treatment of the patients under one year of age makes the groups statistically not comparable. It was felt, due to the severity of the disease in this group, that the change was warranted because of the apparent clinical difference in gastrointestinal irritation between the drugs. No attempt was made to compare treated and control patients statistically.

6. X-ray check on termination of treatment.

7. Follow-up x-ray in seven days on all patients remaining in town.

8. Cold agglutinin and influenze A and B titers were repeated on those children still remaining here.

Method of Treatment and Evaluation.—The dosage of aureomycin and Chloromycetin was 250 mg. initially and 125 mg. every six hours for children up to 15 kilograms in weight, and 500 mg. initially and 250 mg. every six hours for children up to 25 kilograms. The dosage of terramycin was 250 mg. initially and 100 mg. every six hours for children up to 12 kilograms, and 500 mg. initially and 250 mg. every six hours for those up to 25 kilograms. None of the children exceeded this weight. The drugs were mixed with one teaspoon of honey and were taken well by all patients. The course of treatment was five days.

The clinical response to treatment was judged as follows:

1. Excellent: Afebrile in twenty-four hours, cough subsided and patient clinically well in three days or under.

2. Good: Afebrile in forty-eight hours, cough subsided and patient clinically well in five days or under.

3. Poor: Temperature normal in forty-eight hours or under, cough not subsided or patient not clinically well in five days.

Clearing of the pulmonary lesion as shown by x-ray was not taken into consideration in judging response as the time of clearing was extremely variable and did not usually occur for seven to ten days after treatment was completed.

No other treatment was given for the respiratory disease. In patients under one year of age gastrointestinal symptoms, diarrhea with or without vomiting, were present in 65 per cent of cases. Dietary management and parenteral fluids were used as necessary. No drugs were used for treatment of the gastrointestinal symptoms which usually cleared on the second or third day of treatment. This was felt to be a parenteral gastroenteritis secondary to the respiratory infection. Stool cultures were done but no significant organisms were isolated.

Controls.—There were six control cases. A typical case history follows:

CASE 1.—This 2½-year-old girl was seen in the outpatient clinic with a history of a cough without coryza which started on shipboard four days previous and was getting progressively worse. The child had some loss of appetite and increased irritability. Temperature had not been elevated. Physical examination was normal. White blood count was 7,900, polymorphonuclears 41, leucocytes 58, monocytes 3. X-ray showed increased right hilar shadow with minimal infiltration extending into right lower lobe. Diagnosis: Probable atypical pneumonia. She was followed in the hotel by the visiting nurse who reported her condition unchanged for the next two days. On the seventh day she developed a temperature of 101.5° F. and was admitted to the hospital. Physical examination revealed a somewhat sleepy girl who was fussy and whining. There was minimal redness of the posterior pharynx. There were five moist râles in the right lower lobe but the chest was otherwise normal. General physical examination was normal. White blood count was not elevated. X-ray showed increase in the infiltration in the right lung and involvement of left hilus and mid-lung field. Diagnosis: Atypical pneumonia. Hospital course: Her general condition remained unchanged. She ate very little and coughed continually but somewhat worse at night. Steam inhalation gave no notable relief. Her temperature remained elevated, 101.5° to 102.5° F. every afternoon for the next five days. On the fifth hospital day her appetite began to improve and she seemed less irritable. Beginning on the sixth day her temperature became progressively less and she was afebrile on the eighth day. Her clinical condition improved concomitantly with lysis of temperature. Her cough subsided on the eleventh hospital day. On the twelfth day x-ray showed clearing of the left lung. The right hilar shadow was still increased with minimal infiltration in the right lower lobe. Cultures of the nose and throat revealed beta streptococcus and diphtheroids. Cold agglutinins done three weeks after onset were negative. Influenza A and B and Q fever titers were negative.

In the six control cases the average duration of illness from the onset of symptoms to clinical recovery was twenty-six days. X-ray findings did not return to normal for an additional one to four weeks. Fever persisted for an average of 6.5 days (variation from 3 to 14 days) with fall by lysis in all cases. The only purpose of these controls was to obtain a clinical impression of the course of the disease during various periods of the epidemic. There appeared to be no change in severity.

AUREOMYCIN

There were fifty-eight patients treated with aureomycin. Of this number forty-five were febrile (101° F. or over) for twenty-four to forty-

eight hours prior to treatment. There were thirteen patients who were afebrile but clinically had severe cough, irritability, loss of appetite, and malaise in addition to progressive pulmonary involvement by x-ray.

TABLE I. SUMMARY OF RESULTS WITH AUREOMYCIN

RESULTS	FEBRILE 45	AFEBRILE 13	TOTAL 58
Excellent	31	5	36
Good	10	6	16
Poor	4	2	6
Relapses	2	1	3
Reaction to drug	7	2	9

The six patients listed as poor responses to therapy seemed to obtain some early clinical benefit from treatment and were afebrile in thirty-six hours. The improvement was gradual and they were usually well in seven to eight days. Since this improvement may have been coincidental they were considered as treatment failures.

The three patients who relapsed became clinically ill two to four days after discontinuation of the original treatment. Temperatures were 102° F. or over. The cough returned. There was x-ray evidence of increase in pulmonary infiltration in all three patients. One of the patients who relapsed had had an excellent response, one a good response, and one a poor response to aureomycin. The other two were retreated with Chloromycetin with excellent results in both cases.

The only reaction observed to aureomycetin was gastrointestinal irritation. There were seven cases with vomiting and/or diarrhea which did not necessitate discontinuation of the drug. Four of the nine patients were under one year of age. In two other cases the drug had to be discontinued due to vomiting. Therapy was changed to Chloromycetin in both children. This was well tolerated by one child. The other child was not able to retain this drug either.

Case Summaries.—

CASE 2.—A 16-month-old girl had a history of a cough with mild coryza for three weeks. X-ray examination two weeks prior showed right hilar enlargement with suggestive right lower lobe infiltration fanning from the hilus. Twenty-four hours before admission she developed a temperature

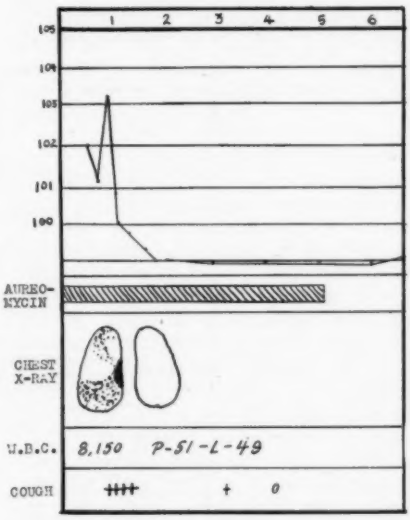

Chart 1 (Case 2).

of 103° F. and became clinically much worse. Physical examination revealed mild coryza, slight pharyngeal redness, and fine moist râles in both bases. White blood count was 8,150, polymorphonuclears 51, leucocytes 49. X-ray showed more marked hilar involvement with considerable increase in the right lower lung field infiltration as compared to the one taken two weeks previously. Hospital course: Aureomycin 250 mg. initially and 125 mg. every six hours was started. She was afebrile in twenty-four hours. Cough was almost gone on the third

day and she was clinically well on the fifth day.

CASE 3.—This 2-year-old boy had had a cough for ten days. He had been hospitalized on shipboard because of a possible pneumonia and treated with penicillin with slight improvement. Two days before admission he developed diarrhea. During the twelve hours preceding admission he had frequent loose stools and a temperature of 104° F. Physical examination: Temperature 103.5° F., hyperemia of the nasopharynx, and mucoid nasal discharge. There were fine râles in the right lower lobe but otherwise normal chest findings. The reand stools were normal. Laboratory findings revealed white blood count 7,400, polymorphonuclears 41, leucocytes 59. Purified protein derivatives first and second strength were negative. X-ray on admission showed bilateral increased hilar shadows with diffuse patchy infiltration most marked in the right lung, but some bilateral involvement. On discharge there was about 50 per cent clearing in the right lung field and no change in the left side. Although there was definite improvement and drop in temperature, a complete clearing of the cough occurred on the eighth day, so this was considered a poor result.

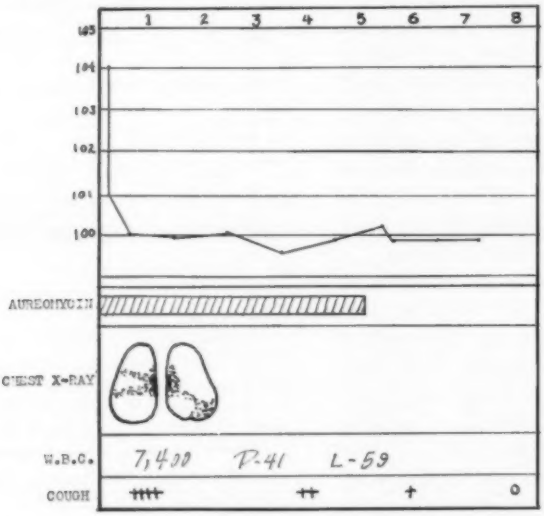

Chart 2 (Case 3).

mainder of the examination was normal. Hospital course: Child was started on aureomycin 500 mg. initially and 250 mg. every six hours. There was gradual improvement in the clinical condition, and diarrhea improved on the third day. Medication was stopped at the end of five days. There was about 75 per cent decrease in his cough at this time and he still had one to two loose stools daily. On the eighth day the cough had subsided

CHLOROMYCETIN

There were sixty-six patients treated with Chloromycetin. Temperature of 101° F. or over had been present for twenty-four to forty-eight hours in forty-nine patients. There were seventeen patients afebrile but who clinically had frequent, severe, prolonged coughing spells, irritability, loss of appetite, and malaise associated with pro-

gressing pulmonary involvement by x-ray.

The four treatment failures again showed apparent early clinical benefit from treatment but complete recovery took seven to eight days and may have been the natural course of the disease. All patients were afebrile in thirty-six hours or under.

TABLE II. SUMMARY OF RESULTS WITH CHLOROMYCETIN

RESULTS	FEBRILE 49	AFEBRILE 17	TOTAL 66
Excellent	37	7	44
Good	10	8	18
Poor	2	2	4
Relapse	2	0	2
Reaction to drug	4	1	5

The two patients who relapsed had temperatures of 103° F. with severe cough and x-ray evidence of increased pulmonary infiltration as compared to discharge films. They had had excellent response to Chloromycetin and were retreated with excellent results.

The drug reactions observed were all gastrointestinal in type and usually mild in nature. One infant had severe vomiting which required discontinuation of Chloromycetin for forty-eight hours after which it was restarted and was well tolerated. This may have been due to the disease as the child was having severe vomiting and diarrhea at the time of admission (see Case 5). The child referred to under aureomycin reactions was also unable to tolerate Chloromycetin.

Case Summaries.—

CASE 4.—This 9-month-old boy had had a cough for three days with audible wheezing for thirty-six hours. He was afebrile. Admission examination: There was a mild mucoid rhinitis; chest was filled with coarse, moist rhonchi, otherwise normal. The white blood count was 7,500, polymorphonuclears 26, leucocytes 74. X-ray showed diffuse fine hazy infiltration involving the entire right lung field and left upper lobe to a lesser extent. Diagnosis: Atypical pneumonia. Hospital course: Temperature was 101° F. the day after admission and 102.4° F. the following day. Procaine penicillin 300,000 units initially and daily had no effect over a three-day period. Chloromycetin 250 mg. initially and 125 mg. every six hours was started on the fourth day of fever with rapid fall within twenty-four hours to normal. There was no clinical improvement on penicillin, but this child was clinically well forty-eight hours after the onset of Chloromycetin therapy. Cold agglutinins were positive $\frac{1}{64}$ ten days after discharge.

CASE 5.—This 7-month-old boy was admitted with a history of a runny nose and two to three loose stools daily for the previous four days. Twelve hours before admission he developed a temperature of 103° F. Vomiting occurred three times in this twelve hours. Physical examination was normal except for a mucoid nasal discharge. Temperature was 102.8° F. The white blood count was 10,900, polymorphonuclears 13, leucocytes 87. X-ray revealed that there was moderate hilar enlargement with a diffuse ground-glass type of fine infiltration involving both lung fields with heaviest involvement in the right lower lobe. Diagnosis: Atypical pneumonia. Hospital course: The child was placed on skim milk. Penicillin 200,000 units every twelve hours was started. Twenty-four hours after admission the child went into moderate peripheral vascular collapse and was mildly dehydrated. Respiratory rate was 32. Chest was filled with wet bronchial râles. Fluids were given by clysis. Penicillin was discontinued. Chloromycetin 250 mg. initially and 125 mg. every six hours was started. The response was dramatic both in clinical improvement and drop in temperature. The vomiting continued, however, and

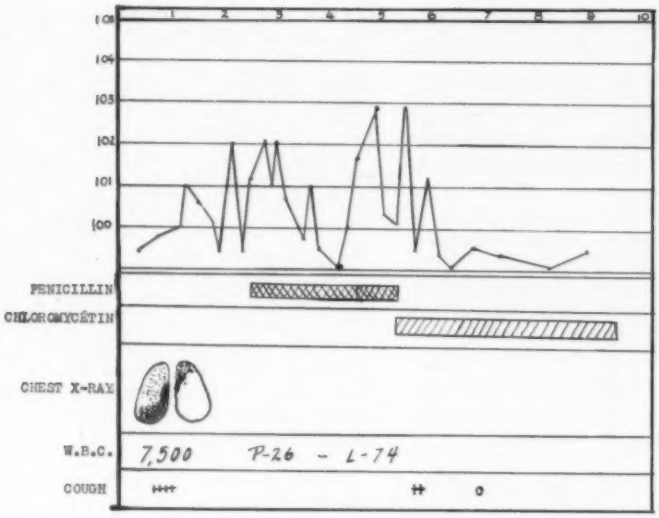

Chart 3 (Case 4).

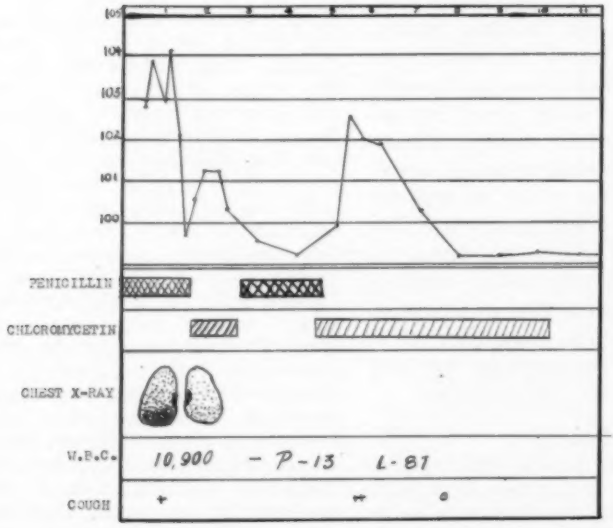

Chart 4 (Case 5).

Chloromycetin had to be discontinued after twenty-four hours. Penicillin was restarted. The vomiting cleared in the next thirty-six hours. In forty-eight hours the child was again febrile and in severe shock with cyanosis and respiratory rate of 56 but no dehydration. Intravenous fluids and blood were given in repeated small quantities with some improvement. Chloromycetin was again started in the same dosage. There was no vomiting. The child was clinically much improved in thirty-six hours. Cough disappeared and physical examination of the chest was normal in forty-eight hours. Diarrhea cleared and he was on a normal diet at the end of the third day of treatment. He was discharged after seven days of treatment. The x-ray was clear five days after discharge. Respiratory symptoms never were prominent in this child although his x-ray findings were marked. The gastrointestinal symptoms did not clear until his pulmonary disease was controlled.

TERRAMYCIN

There were nineteen patients treated with terramycin. The summary of the results is shown in Table III.

TABLE III. SUMMARY OF RESULTS WITH TERRAMYCIN

RESULTS	FEBRILE 14	AFEBRILE 5	TOTAL 19
Excellent	8	3	11
Good	5	2	7
Poor	1	0	1
Relapse	0	0	0
Reaction to drug	1	0	1

The one child who had a poor response was well at the end of the sixth day.

The absence of any relapses is of no significance due to the small number of cases.

One patient appeared to have some gastrointestinal irritation from terramycin. This 18-month-old child had a mild diarrhea on admission which was worse while on treatment and cleared forty-eight hours after the five-day course of therapy was completed. No other reactions were observed.

Case Summaries.—

CASE 6.—A 2½-year-old boy had been coughing for two and one-half weeks. On the day before hospital admission the cough was very severe and he was feverish, fussy, and had a decrease in appetite. Examination showed an acutely ill boy with a temperature of 103.6° F., slight nasal discharge, and a deep heavy cough. The lungs were clear to auscultation. A clear x-ray showed an increase in hilar markings and definite bilateral lower lung field infiltrations. The white blood count was 5,800, polymorphonuclears 67, leucocytes 33. Cold agglutinin was positive 1/32. He was watched for twenty-four hours, but became somewhat worse and his temperature began rising after dropping to normal soon after admission. Terramycin was started on the second hospital day. Dosage was 500 mg. initially and 250 mg. every six hours for five days, a total of 5.5 Gm. Within thirty-six hours his temperature became normal and stayed normal. He looked a lot better, began to play and eat better. On the third day of therapy his cough definitely subsided. He went on to an uneventful recovery and was discharged as well after five days of therapy.

CASE 7.—This 2½-year-old girl was apparently well until the day before hospital admission when she developed a severe cough, fever, and loss of appetite. On the day of admission the cough was almost constant, deep, and croupy. Examination showed an acutely ill child with a temperature of 102.8° F. There was a mild aphthous stomatitis. The chest was clear on admission in spite of the severe croupy cough. The rest of the physical examination was normal. X-ray of the chest

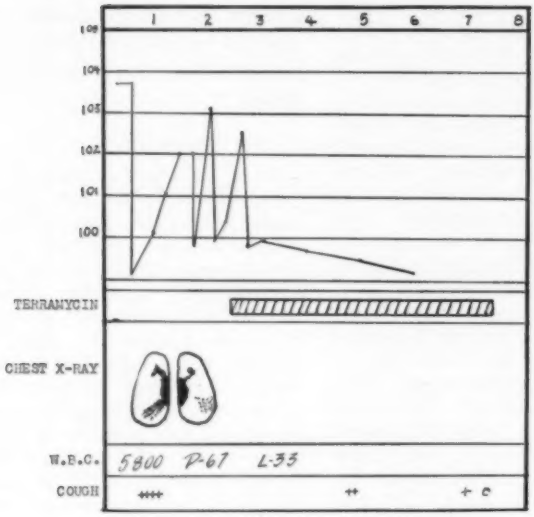

Chart 5 (Case 6).

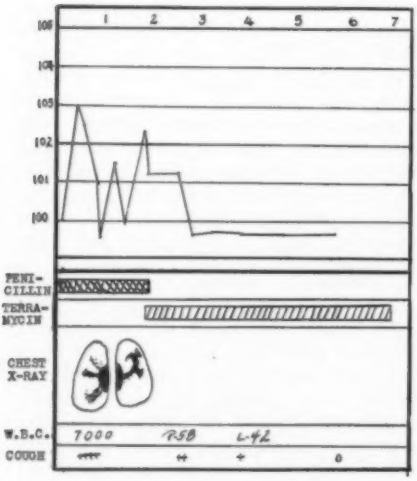

Chart 6 (Case 7).

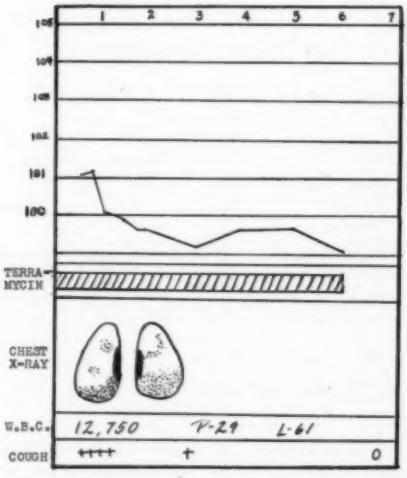

Chart 7 (Case 8).

showed an increase in hilar shadows with infiltration of the right middle and right upper lobes and some infiltration in the left upper lobe. The white blood count was 7,000, polymorphonuclears 58, leucocytes 42. On admission she was placed on penicillin 200,000 units every twelve hours. Her fever continued and she became worse. It was necessary to put her into a croup tent. Auscultation of the chest at this time revealed "sticky" râles over the entire right lung. Respiratory rate was 42 and respirations were somewhat shallow. On the third hospital day, as the child continued to do poorly, terramycin was started. Dosage was 500 mg. initially and 250 mg. every six hours, a total of 5.5 Gm. The response was excellent, as she became afebrile in twenty-four hours, began to eat, coughed less, and breathed easier. On the fifth day she was able to be out of the croup tent, played with toys, and coughed rarely. On the third day of treatment the cough was entirely gone. The child was discharged well after five days of treatment.

CASE 8.—A 9-month-old girl had a "cold" three weeks prior to admission, consisting of cough, slight coryza, and occasional loose stools. The night before admission she coughed incessantly. Examination revealed a drowsy, acutely ill baby, slightly dehydrated with mild coryza, deep heavy cough, and respiratory rate between forty and fifty per minute. The temperature was 101.2° F. Lungs were clear to auscultation. X-ray of chest showed increased hilar markings with bilateral patchy infiltration of the lower lobes. The white blood count was 12,750, polymorphonuclears 29, leucocytes 61. Terramycin was started on admission. Dosage was 250 mg. initially and 100 mg. every six hours for seven days; a total of 2.9 Gm. was given. A clysis was given on admission. In eighteen hours the child was afebrile. On the second day of therapy her cough definitely subsided, she looked well, and began eating with interest. She was discharged well after seven days of treatment.

COMPARISON OF CASES

In order to evaluate the results of treatment statistically it is necessary that the cases be comparable. It is felt that the three groups are as comparable as it is ordinarily possible to obtain except for age distribution which was weighted by choice of patients. The higher percentage of children under one year of age in the Chloromycetin and terramycin groups is the result of the previously mentioned changes in method of treatment.

The age distribution of the treated patients is shown in Table IV.

The duration of symptoms is calculated from the onset of cough or respiratory symptoms to the first day of therapy. The approximate distribution is as shown in Table V.

TABLE IV. AGE DISTRIBUTION

	6 MO.	12 MO.	18 MO.	24 MO.	3 YR.	4 YR.	5 YR.
Aureomycin	8	15	8	11	7	5	4
Chloromycetin	18	20	10	8	4	3	3
Terramycin	8	2	1	5	0	3	0

TABLE V. DURATION OF SYMPTOMS IN DAYS PRIOR TO ADMISSION OF DRUGS

	4 DAYS	7 DAYS	10 DAYS	14 DAYS	21 DAYS	AVERAGE
Aureomycin	17	14	15	8	4	8.8
Chloromycetin	20	16	19	7	4	8.4
Terramycin	3	5	4	4	3	11.1

TABLE VI. TEMPERATURE DISTRIBUTION

	101°	102°	103°	104°
Aureomycin	20	7	12	6
Chloromycetin	20	9	10	10
Terramycin	4	3	4	3

TABLE VII. SUMMARY OF TREATMENT RESULTS

	EXCELLENT	GOOD	POOR	RELAPSE	REACTION TO DRUG
Aureomycin	36	16	6	3	9 15.5%
Chloromycetin	44	18	4	2	5 7.6%
Terramycin	11	7	1	0	1 5.2%

The temperature distribution at the onset of treatment for the febrile patients is shown in Table VI. All temperatures are rectal.

Summary of the treatment results is shown in Table VII.

DISCUSSION

That the disease in young infants is a serious one and does not present the usual clinical picture is well illustrated by Cases 4 and 5. The respiratory symptoms may be minimal, suggesting only a slight cold, or they may be a severe cough resembling pertussis. The temperature is frequently not greatly elevated and may be normal. Diarrhea with or without vomiting is present in almost all patients under 6 months of age and in 65 per cent of all children under one year of age.

These infants may appear quite well except for a mild diarrhea associated with a runny nose for many days. Sudden collapse of the infant with temperature of 104° to 105° F. or a subnormal temperature may then occur and one is faced with a critically ill patient. The diagnosis is usually possible before this acute period if it is considered. Localized râles are present in the majority of patients. The x-ray findings are usually those of hilar enlargement and a diffuse, very fine infiltration resulting in a ground-glass appearance with almost no normally aerated lung to be seen. In this age group it is rare to see lobar or lobular localization or discrete areas of infiltration. No etiological diagnosis can be made from the x-ray. Clinical observation must complement the use of x-ray in deciding the type of pneumonitis. The combination of upper respiratory symptoms and gastroenteritis in infants and young children should bring the diagnosis of atypical pneumonia to mind.

Thirty-five of the patients in this series, whose treatment was based on x-ray findings and clinical symptoms, developed no fever. Because of the epidemic conditions, most children were seen within forty-eight to seventy-two hours after the onset of any respiratory symptoms. At this time chest x-rays were done on all such patients and about 20 per cent of these (a total of 174 patients) had definite x-ray evidence of pneumonia without elevation of temperature. These patients were followed daily. There were eighty-seven patients who subsequently developed fever and are in-

cluded in the treated febrile cases. Any factor which lowered the child's resistance, such as loss of sleep, etc., frequently was sufficient to cause a febrile response, and progression of x-ray findings in a child who had been afebrile had minimal infiltration by x-ray, and mild clinical illness. Eighteen of the children with fourteen to twenty-one days of illness preceding therapy fall into this group. The thirty-five afebrile patients previously mentioned were treated because their clinical condition and x-ray findings were getting progressively worse. The remaining fifty-two patients were untreated, since their clinical symptoms were less severe and they were followed as outpatients. Clinical recovery for this untreated group averaged twenty-five days from the onset of first symptoms.

The varying degrees of clinical severity of the disease are more noticeable under epidemic conditions but they also occur under normal circumstances.

The percentage of excellent and good results shows no significant difference: aureomycin 90 per cent, Chloromycetin 94 per cent, and terramycin 94 per cent. No difference in relapse rate is noted between aureomycin and Chloromycetin. No relapses were seen in the patients treated with terramycin but this is of no significance because of the small number.

There is a definite difference in reaction rate: aureomycin 15.5 per cent, Chloromycetin 7.6 per cent, and terramycin 5.2 per cent. This difference is of considerable importance in young children and infants since gastrointestinal disturbances, diarrhea, and vomiting are already present in a high percentage of patients.

The smaller series treated with terramycin makes the drawing of definite conclusions impossible. It is our clinical impression, supported by the presented data, that terramycin is the drug of choice in the treatment of atypical pneumonia in infants and children. Chloromycetin would seem to be almost as satisfactory and further experience with terramycin will be necessary before a final conclusion can be drawn. Aureomycin would seem to be the least valuable due to the higher incidence of gastrointestinal side effects.

SUMMARY

A series of 143 patients with atypical pneumonia treated with aureomycin, Chloromycetin, and terramycin is evaluated.

Terramycin is felt clinically to be the drug of choice in the treatment of atypical pneumonia in infants and children.

Attention is called to the severity of the disease in infants.

The ocurrence of afebrile cases of atypical pneumonia is discussed.

Note: Since preparation of the original paper, an additional seventeen patients have been treated with terramycin. Excellent or good results were obtained in sixteen cases. There was one reaction to terramycin consisting of a mild diarrhea which cleared after treatment was completed.

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PAROXYSMAL TACHYCARDIA

Report of Two Cases in Infants Under One Month of Age

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PAROXYSMAL tachycardia is being recognized in early infancy with increased frequency, yet cases in infants under one month of age are comparatively rare. It is the purpose of this paper to add two additional cases, one with many recurrences.

CASE REPORTS

Case 1.—A 13-day-old white male infant was admitted to St. Joseph Infirmary on July 31, 1947, at 9:15 P.M. with the chief complaint of "heart beats too fast." According to the parents he seemed perfectly well up to three days prior to admission. At that time he had "labored breathing," but no cyanosis, fever, or gastrointestinal complaints. Two days prior to admission the mother noted that the infant's "heart beat fast." About eight hours prior to admission he was seen by the family physician who told the parents the heart was very fast.

The delivery was described as breech extraction with some difficulty, and the father stated that the child was cyanotic when seen coming from the delivery room. The birth weight was 9 pounds, 9½ ounces. Feedings were entirely by breast. The remainder of the past history and family history was completely normal.

Physical examination on admission revealed a temperature of 98.4° F., respirations 48 per minute, pulse estimated between 200 and 210 per minute. The weight was 9 pounds, 12 ounces. The skin revealed an ashen cyanosis with extreme pallor of the nail beds. Examination of the heart revealed no murmurs but a questionable apical thrill. Breathing was slightly labored but no râles could be heard. The liver could be palpated 3 cm. below the right costal margin. The remainder of the physical examination was entirely normal. The clinical impression on admission was paroxysmal tachycardia with possible congenital heart disease.

Laboratory examination revealed an electrocardiogram rate (Fig. 1) of 160 per minute which was interpreted as paroxysmal auricular tachycardia and right ventricular strain. This rate was much less than had been estimated previously but re-examination of the heart immediately after the electrocardiogram confirmed the finding that the heart had decreased in rate. Roentgenogram of the chest (Fig. 2) on July 31, 1947, and a repeat film on August 1 revealed widening of the cardiac and supracardiac shadow. Some atelectasis was apparently present. Urinalysis was normal. The blood count revealed 6,150,000 red blood cells per cubic millimeter with a hemoglobin of 120 per cent, 22,800 white blood cells per cubic millimeter with a differential of 51.5 per cent neutrophiles, 46 per cent lymphocytes, 1.5 per cent myelocytes, and 1 per cent basophiles.

Since I had used digitalis previously[1] in the treatment of paroxysmal tachycardia, 1.5 grains Digifolin were given subcutaneously two hours after admission.

The heart rate was estimated every hour during the night and it was found to range from 146 to 218 beats per minute. The following morning the heart rate was 130 beats per minute. There was some question of a systolic apical cardiac murmur, but none was ever definitely heard.

From the Department of Pediatrics, University of Louisville School of Medicine.

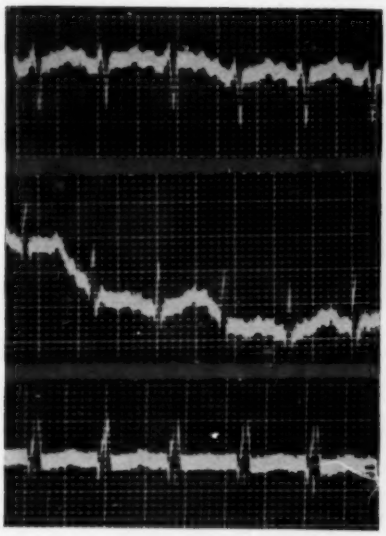

Fig. 1.

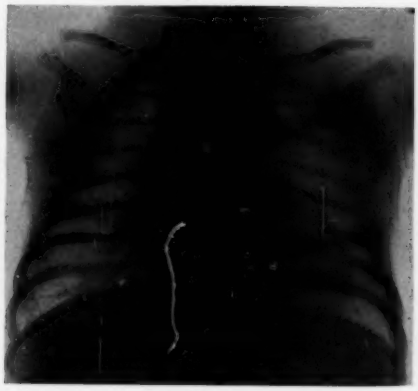

Fig. 2.

Fig. 3.

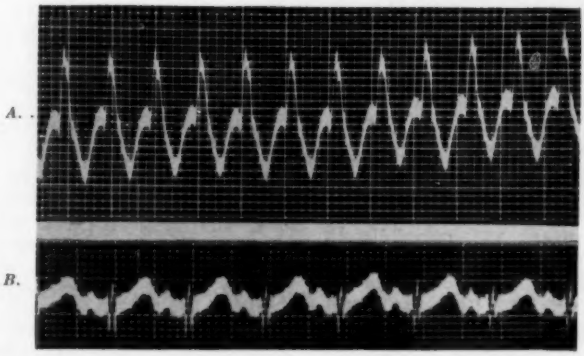

Fig. 4.

The child was carefully observed but the heart rate was never found to be over 120. No further therapy was instituted and the child was discharged Aug. 3, 1947.

The mother was instructed as to counting the heart rate, and on Aug. 6, 1947, the rate became too fast for her to record. The child was placed in the Children's Hospital immediately. The physical examination at this time revealed a temperature of 99.6° F., respirations 38 per minute, and heart rate of 200 plus per minute. The extremities revealed slight cyanosis. One grain (0.065 Gm.) of Digifolin was given immediately subcutaneously. The following day the heart rate had dropped to 132 per minute. Repeat electrocardiogram on August 8 was entirely normal with a rate of 140 per minute and roentgenogram (Fig. 3) of the chest was interpreted as negative. Except for a period of transient diarrhea the second hospitalization was uneventful.

August 11, three days later, the mother again observed the heart to be fast. The child was brought to the office where the cardiac rate was found to be extremely rapid. Electrocardiogram revealed a rate of between 260 and 280 per minute and was interpreted as paroxysmal tachycardia (Fig. 4, *A*).

Since the patient had responded to digitalis previously but had immediate recurrences, it was decided to give quinidine sulfate 2 grains orally. The infant vomited immediately, but within six hours the heart rate was again normal.

This child was seen August 18. Examination of the heart was entirely normal; electrocardiogram revealed a rate of 140 per minute (Fig. 4, *B*).

On August 26 (at the age of 6 weeks) the heart rate was 110 per minute, and the infant had gained to 12 pounds, 9 ounces.

On September 15, while the mother was giving the child a bath, she again noted the tachycardia of over 200 per minute. The child became listless, lifeless, and his pupils became pinpoint. Again 2 grains of quinidine were administered orally and repeated in four hours with the tachycardia subsiding.

Again on September 18 another paroxysm of tachycardia occurred. Two doses of quinidine were administered, and on physical examination the following day the heart rate had returned to 160 per minute. In view of the recurrence, digitalis ¼ grain was administered orally as a prophylaxis for ten days.

An electrocardiogram by Dr. Woodford B. Troutman, October 1, was interpreted as normal with a rate of 120 per minute.

The infant was seen numerous times in the interim, and in spite of an ischiorectal abscess which had to be incised and drained, no tachycardia occurred until Feb. 11, 1948. Digitalis was again administered orally ¼ grain twice daily for two days, then ¼ grain for two days. This same treatment had to be repeated May 28 for another paroxysm of tachycardia.

Except for two bouts of otitis media which responded to penicillin therapy, erythema multiforme, and measles, he remained free of cardiac symptoms until April 19, 1949, at which time digitalis was again administered. He has been seen at frequent intervals, and other than another infection of otitis media, which required a paracentesis of the tympanic membrane, he has had no difficulty.

Roentgenogram of the chest Jan. 10, 1950, showed a somewhat transverse type of shadow. The ratio to the chest was 9.9 cm. to 18.2 cm.

On March 27, 1950, under general ether anesthesia, he had a successful tonsillectomy and adenoidectomy without cardiac complications. In April, at the age of 2 years, 8 months, his weight was 35 pounds (16 kilograms) and his height, 37¼ inches (94 centimeters). He has been immunized for diphtheria, pertussis, tetanus, and successfully vaccinated without reactions.

CASE 2.—This 18-day-old infant was admitted to the Kentucky Baptist Hospital, Jan. 10, 1948, with the chief com-

plaint as given by the parents of "trouble getting her breath and turning blue."

The infant was born at St. Mary and Elizabeth Hospital, Dec. 23, 1947. The hospital stay was uneventful and she was discharged on her sixth hospital day on an evaporated milk, water, and carbohydrate formula. Because of loose stools and vomiting shortly after getting home, the formula was diluted. The vomiting persisted and atropine 1/1,000 grain was administered before each feeding. After two doses, the temperature rose to 105° F. rectally. Breathing difficulty soon followed. Discontinuance of the atropine brought about relief of the high fever, but a low-grade temperature and rapid respiration continued.

Fig. 5.

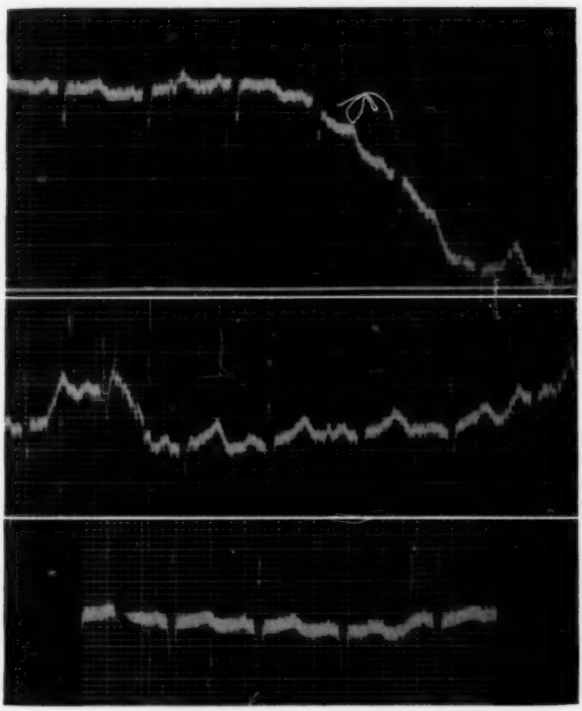

Fig. 6.

I first saw the infant at home Jan. 9, 1948. At that time the temperature was 101° F. rectally, respirations 62 per minute, heart rate 120 per minute without a murmur. The remainder of the complete physical examination was entirely normal. Since nothing except the rapid respiration with slight respiratory grunt could be found, sulfadiazine was administered 0.1666 Gm. orally every four hours five times each twenty-four hours.

The following morning, January 10, according to a telephone report by the mother, the infant seemed only slightly better, and it was decided to give penicillin. By the time a visiting nurse could be found to administer intramuscular penicillin the temperature rose to 104° F. and the infant became cyanotic. Due to the change in her condition she was admitted to the hospital at 3:55 P.M.

The remainder of the past history and the family history was noncontributory.

Physical examination on admission to the hospital revealed an 18-day-old infant in acute respiratory distress with marked cyanosis. The temperature was 104.2° F., respirations 55 per minute, and pulse too rapid to count. The skin was extremely dry and desquamating. The thorax showed bilateral and equal expansion with coarse breath sounds throughout. The heart was too rapid to count, but the rate was estimated at about 200 per minute. No murmurs could be heard. The liver, kidneys, and spleen could not be palpated. Laboratory studies revealed a red blood cell count of 4,700,00 per cubic millimeter with hemoglobin of 14.0 Gm. per 100 c.c. of blood, and white blood cell count of 24,000 per cubic millimeter with 86 per cent polymorphonuclear leucocytes, 24 per cent lymphocytes, and 1 per cent monocytes. The carbon-dioxide combining power was 42 volumes per cent. The urinalysis revealed 20 to 30 white blood cells per high-power field and was otherwise negative. A roentgenogram of the chest was interpreted as normal. The Lead II of the electrocardiogram (Fig. 5) revealed a rate of 190 to 200 per minute, with a diagnosis of paroxymal supraventricular tachycardia.

While awaiting reports, the baby was given intramuscular penicillin 50,000 units every three hours, oxygen, and, to reduce temperature, symptomatic therapy consisting of alcohol sponges and tepid water enemas. Six hours after admission 1 grain of digifolin was given intramuscularly. A solution of 250 c.c. of 2.5 per cent glucose in normal saline was given subcutaneously into the thighs.

The following day, January 11, the heart was still rapid, estimated at 174 per minute. Another injection of Digifolin ½ grain was administered and 75 c.c. of sodium lactate solution was given intravenously. The respirations were still rapid, 62 per minute, and the temperature remained elevated to 102° F. At 9:00 P.M. the heart was still rapid and another ½ grain of Digifolin was given. The following day, January 12, the heart rate dropped to 120 per minute. The penicillin was continued until discharge on Jan. 17, 1948, even though the temperature and pulse remained normal. No further Digifolin therapy was necessary.

A repeat electrocardiogram Jan. 12, 1948, revealed a rate of 160 per minute with right axis deviation. (Fig. 6.) Tracing made Feb. 10, 1948, showed ventricular rate of 110 to 120 per minute. In comparison with electrocardiogram made January 12, there was now noted a tendency to right axis deviation but not as prominent as in the tracing of January 12. The T waves were distinct, upright, and of normal appearance. On January 12 T waves were of low voltage in Leads I and III.

She has been checked at frequent intervals and has had no recurrence of the tachycardia. She was last seen June 30, 1950, at which time she weighed 30 pounds (13.6 kilograms). She has been immunized for diphtheria, tetanus, and pertussis, and re-

ceived a successful vaccination for smallpox without reaction.

COMMENT

The first patient (Case 1) was rather a typical case from the beginning, but the number of recurrences makes it unusual. The second patient (Case 2) was seen at home the day prior to admission to the hospital and was apparently observed between attacks.

CONCLUSION

Two cases of paroxysmal tachycardia in infants under one month of age with recovery are herein reported.

The author wishes to express his appreciation to Dr. W. B. Troutman for the electrocardiographic interpretations.

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EXCHANGE TRANSFUSION FOR FETAL ERYTHROBLASTOSIS

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FAMILIAL icterus gravis of the newborn infant was first arrested by early exsanguination transfusion by A. P. Hart in 1925.[1] Assuming that some toxin circulating in the blood was the cause of the difficulty, Hart performed an exsanguination transfusion in the hope of removing a sufficient amount of toxin to prevent the progress of the disease. Synchronous transfusion of the saphenous vein at the ankle and exsanguination from the anterior fontanel, using group specific blood, was followed by uneventful recovery. Six previous babies of this mother had died and a living sister 12 years of age was mentioned as suffering with chorea, probably kernicterus. Twenty-one years later, in 1946, after the toxin had been identified as the hemolyzing antibodies, such as produced by the Rh factor, H. Wallerstein[2] introduced the technique specifically for the treatment of severe fetal erythroblastosis as we now know the syndrome. L. K. Diamond, in 1946, contributed a more simple method of withdrawal from and replacing the blood into the inferior vena cava through a polyethylene catheter introduced via the umbilical vein, although he did not publish the description of the method and his excellent results until 1948.[3] The technique of exsanguination from the radial artery, transfusion into the saphenous vein at the ankle,[4] and heparinization of the infant was first described in the literature by Wiener and Wexler in 1946.[5] Arnold and Alford,[6] considering the use of the umbilical vein route dangerous after twelve hours of age because of possible disengaging of clots, introduced an alternative method of reaching the inferior vena cava with a plastic catheter inserted into the exposed great saphenous vein in the groin. They objected to heparinization because of the hemorrhagic tendency of erythroblastotic babies.

The replacement of the infant's blood by compatible nonantigenic blood is now the accepted treatment for severe erythroblastosis. The preferred route is the umbilical vein. (Fig. 1.)

The great saphenous vein is the alternative route if the catheter cannot be introduced into the umbilical vein or after twelve to twenty-four hours when the umbilical vein may be thrombosed. (Fig. 2.)

It has been demonstrated that the exchange of twice the blood volume will result in the removal of about 85 per cent of the infant's blood.[5] The blood volume of the average newborn infant is about 250 c.c.[2] Five hundred cubic centimeters of blood transfused into the baby and 450 to 500

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c.c. withdrawn will usually effect removal of sufficient blood to halt the progress of the disease. The explanation of therapeutic failures remains obscure.

Fig. 1.—Plastic catheter inserted into umbilical vein leading to inferior vena cava. (Diamond.)

Fig. 2.—Plastic catheter inserted into saphenous vein and passed along femoral and iliac veins to inferior vena cava. (Arnold and Alford.)

An apparatus is here presented which accomplishes the exchange of the blood with a minimum of interference with blood flow which commonly is responsible for technical difficulties due to congealing. The parts are shown assembled in Fig. 3.*

The apparatus is handled by one operator with few mechanical maneuvers.

The items to be assembled are:†

- 2 10 c.c. Record transfusion syringes, Luer tip.
- 2 2-way glass valves.
- 3 7-inch plastic catheters, 20 gauge.
- 2 3-way metal stopcocks.
- 2 19 gauge special transfusion needles, stainless steel.
- 2 Sections of Latex surgical tubing, one inch long.
- 1 Plain sinker.
- 1 Section tubing 10 inches long.
- 1 Filter sinker.
- 1 Section tubing 15 inches long.
- 1 Solution bowl, stainless steel, for rinsing transfusion syringe in heparin-saline solution.
- 2 500 c.c. Ehrlenmeyer flasks.

The parts to be sterilized by immersion in Zephiran Chloride aqueous 1:1,000 solution for 12 hours:

- 2 10 c.c. Record syringes, Luer tip.
- 2 2-way glass valves.
- 3 7-inch plastic catheters, 20 gauge.

The parts to be sterilized by boiling or autoclaving:

- 2 3-way metal stopcocks. } assembled
- 2 19 gauge blunted short bevel needles. } assembled
- 2 Sections of Latex surgical tubing (5/32" × 3/64") one inch long } assembled
- 1 Plain sinker } assembled.
- 1 Section tubing 10 inches long. } assembled.
- 1 Small solution basin.
- 2 500 c.c. Ehrlenmeyer flasks.

*As exhibited at the Eastern Area Meeting of the American Academy of Pediatrics, March 30 to April 1, 1950.

†Apparatus available through Ringler-Rados Surgical Corporation, 3958 Broadway, New York 32, N. Y.

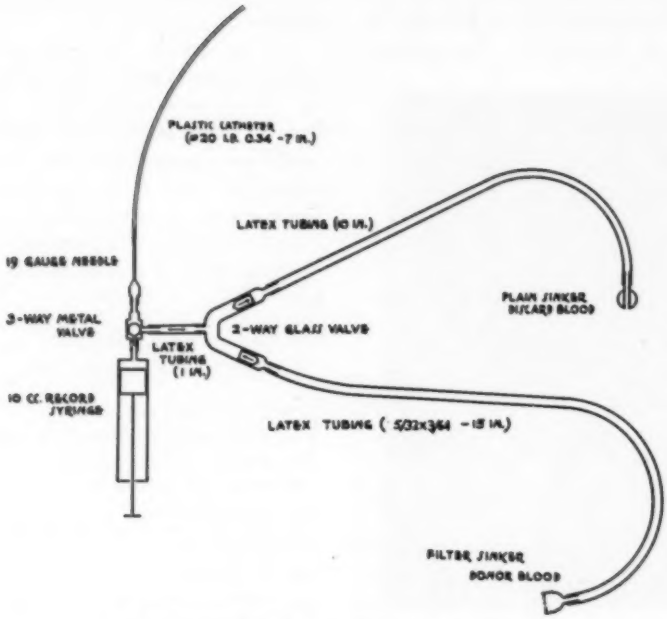

Fig. 3.—Schematic drawing of assembled apparatus.

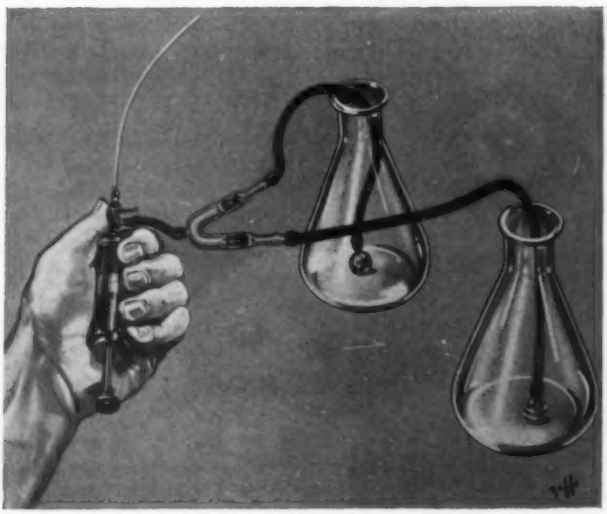

Fig. 4.—Assembled apparatus ready for use.

Rinsing solution—1 c.c. heparin (1,000 units per cubic centimeter) in 100 c.c. normal saline.
Calcium gluconate 10 per cent solution, 5 c.c. ampule.
Silk ligature thread.
Blood Group Specific Substances A and B. 10 c.c.—to be added to Group O donor blood if blood of same group as infant is not available.[8]

THE TECHNIQUE

The apparatus is assembled and loaded with citrated blood with the three-way stopcock set in the "off" position before the introduction of the catheter into the vein. The donor flask may be loaded by direct collection and citrating or by allowing citrated blood to gravitate into it from a suspended blood bank flask. A suspended flask cannot be used directly because the blood will gravitate through the glass valve of the apparatus into the discard flask.

If the possibility of an exchange transfusion is anticipated, the obstetrician is requested to clamp or ligate the umbilical cord two to three inches proximal to the umbilicus. Amputation about an inch from the umbilicus will expose the end of the umbilical vein for insertion of the plastic catheter. The vein can be identified as the largest of the three umbilical vessels. Grasping the edge of the orifice with a fine-toothed forceps or small hemostat clamp and gentle traction downward will enable easier insertion of the catheter. At four to five inches the blood will drip freely. A ligature is applied firmly about the cord.

If the umbilical route is not considered advisable, the saphenous vein may be exposed in the middle of the upper thigh one-half to one inch distal to the inguinal ligament. A small opening is made with a fine scissors or a pointed knife blade. Introduction of the catheter may be facilitated by bevelling its tip and by grasping of the proximal edge of the opening into the vein with a fine-toothed forceps. Occasional obstruction to the passage of the catheter due to venous spasm subsides spontaneously in a few moments.

A ligature is applied about the proximal portion of the vein about the catheter, another about the portion of the vein distal to the insertion of the catheter to control bleeding. Both ligatures are removed at the termination of the procedure.

If the umbilical vein has been used, the catheter is withdrawn and a dry dressing applied. If the saphenous vein has been employed, the ligatures are removed and the wound edges are approximated with two small butterfly adhesive tape strips. A pressure pad of gauze is held firmly in place by a figure-of-eight bandage about the thigh and abdomen.

The needle is inserted into the catheter and the procedure is started by the instillation of 10 c.c. of donor blood. Nine cubic centimeters of infant blood is withdrawn to allow for a positive balance to correct anemia. The setting of the stopcock will direct the donor blood automatically to the infant and the infant blood to the discard flask.

At every 70 to 100 c.c. of blood it is advisable to instill 1 c.c. of 10 per cent calcium gluconate solution to control tetany. The stopcock is set at the "off" position, the 10 c.c. Record syringe is detached for rinsing in the heparin-saline solution, and the calcium instilled from a hypodermic syringe slowly. One to 2 c.c. of hep-

arin-saline solution is drawn into the Record syringe after rinsing, a small amount is passed into the catheter, the remainder is directed into the discard side of the apparatus to discourage clotting of the infant's blood.

Fifty strokes of the Record syringe will accomplish the exchange of 450 to 500 c.c. of blood and allow a positive balance for correction of anemia if indicated.

The instillation strokes of the syringe and other data incidental to the procedure should be recorded by an assistant or observer.

An antibiotic may be given prophylactically.

Early recognition of the syndrome and prompt exchange transfusion is imperative in the care of severely affected infants. Such infants may be the last viable baby the mother may be able to produce and they are deserving of the utmost and prompt consideration. The procedure should be reserved for infants of mothers who present a history of sensitization by previous pregnancy or administration of antigenic blood and who demonstrate clinical and hematological evidence of erythroblastosis.

The following considerations have been accepted as leading to the need for exchange transfusion.

INDICATIONS DURING PREGNANCY

Rh (d) negative mother } 92 per
Rh (D) positive father } cent.

ABO or other incompatibility.

Positive Indirect Coombs' Test in the first trimester indicative of probable severe involvement.[7]

Increasing titer of Coombs' Test during second and third trimesters indicative of involvement.[7]

History of previous sensitizing pregnancy.

History of previous administration of sensitizing blood.

INDICATIONS AT DELIVERY OF INFANT

Icteric amniotic fluid.

Large pale placenta.

Icterus of infant.

Pallor.

Hemorrhagic manifestations.

Edema.

Hepatosplenomegaly.

Anemia—hemoglobin of less than 15 Gm. and red blood cell count of less than 5 million indicates relative anemia for the newborn infant.

Positive Direct Coombs' Test of infant's blood by heel puncture more reliable than cord blood.[7]

Erythroblastemia—count in excess of 20 per 100 white blood cells.

INDICATIONS DURING NEONATAL PERIOD

Increasing icterus.

Decline of hemoglobin and erythrocytes.

Increase of erythroblasts.

Toxicity as indicated by listlessness, weakness, respiratory distress.

Hemorrhagic manifestations.

HEMATOLOGICAL CONSIDERATIONS

Donor blood preferably same group as infant and Rh (d) negative. (Blood from female donors may be favored.)[8]

Group O, Rh (d) negative donor blood if group specific blood not available.

Freshly drawn blood administered soon after drawing preferred.

Positive balance beneficial because of usual anemia—administration of 500 c.c. and withdrawal of 450 c.c. Accomplished by instilling 10 c.c. for each 9 c.c. withdrawn.

TECHNICAL CONSIDERATIONS

Umbilical vein preferable to 24 hours of age if thrombi are not evident.

Saphenous vein by dissection advisable if umbilical vein too tortuous or after 12 to 24 hours of age.

Syringe to be rinsed with heparin solution (1 c.c. of 1,000 units per cubic centimeter in 100 c.c. of normal saline) about every ten strokes to prevent sticking. One cubic centimeter to be instilled through infant and discard portions of apparatus to discourage clotting at time of rinsing.

For control of tetany due to sodium citrate in donor blood, 1 c.c. of calcium gluconate to be instilled into infant through catheter from a hypodermic syringe at time of rinsing, more often if indicated by symptoms.

Ten subic centimeters of Blood Group Specific Substances A and B Solution (Witebsky) to be added to donor blood if Group O.[9, 10]

SUMMARY

The historical development of the procedure of exchange transfusions is reviewed.

The methods of exchanging blood are described.

An apparatus for the performance of the procedure is described.

The indications for exchange transfusions in the treatment of erythroblastosis are presented.

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FRAGILITY OF RED BLOOD CELLS FROM NEWBORN INFANTS AND CHILDREN WITH CYANOTIC CONGENITAL HEART DISEASE

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IN STUDYING the adaptive mechanisms that permit children with cyanotic heart disease to tolerate low oxygen saturations of the arterial blood, an investigation of the possible similarities between fetal blood and the blood of such patients seemed indicated. Since it is well known that newborn animals can survive anoxia for longer periods than adult animals, it seemed possible that children with cyanotic heart disease might have a persistance of that fetal mechanism.

Previous investigators had shown that the oxygen dissociation curves on the blood from such cyanotic children was to the right of the normal adult,[1] and that the blood from newborn infants was to the left.[2] In a previous communication,[3] we showed that the carbonic anhydrase content of the blood of such cyanotic children was not low, as is found in fetal blood, but was normal or increased. After 6 months of age it was proportional to the red cell mass.

Goldbloom and Gottlieb reported a marked increase in the red cell fragility of newborn infants.[4] Booth demonstrated that acutely induced prolonged anoxia in dogs produced increased fragility of the red cells.[5] In light of the observations of Goldbloom and Gottlieb, and of Booth, fragility studies on the red blood cells from such cyanotic children seemed indicated. This report concerns the observations on the blood from twenty-seven children with cyanotic congenital heart disease and from ten newborn infants.

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This work was performed under a cooperative agreement between the University of Minnesota and the National Heart Institute, U. S. Public Health Service, Bethesda, Md.

MATERIALS AND METHODS

All of the children with cyanotic congenital heart disease were seen and studied at the University Hospitals. Their arterial oxygen saturations ranged from 15 to 75 per cent. The newborn bloods were collected in double oxalated tubes from the umbilical cord before the placenta had separated from babies delivered at St. Barnabas Hospital in Minneapolis. The red cell fragilities were done on a Junior Coleman Spectrophotometer using initially the method of Suess and associates.[6] This method involved reintroducing a pipette into the oxalated sample of blood so many times that hemolysis of the cells took place from this maneuver alone, as seen in Fig. 1. The technique was thus modified so that the blood for all the tubes was drawn up into a syringe upon which was fastened a No. 20 gauge needle. One drop of blood was then quickly delivered into each of the tubes containing the various dilutions of saline. By using this method, no significant amount of hemolysis was produced by

the technique itself. The per cent of hemolysis or the hemolytic increment obtained by this technique was then plotted along the ordinate and the decreasing strengths of saline along the abscissa according to the following manner described by Suess:[6]

1. By using conversion tables, the spectrophotometer readings on each tube were changed into grams of hemoglobin liberated.

In order to determine the effect of the oxygen content of the blood on the cell fragility, blood obtained from several severely cyanotic children was tested both unoxygenated and after being oxygenated in an oil-lined flask for five minutes. Red blood cell counts on the newborn infants were done on a double-oxalated specimen obtained from the umbilical cord before the placenta had separated.

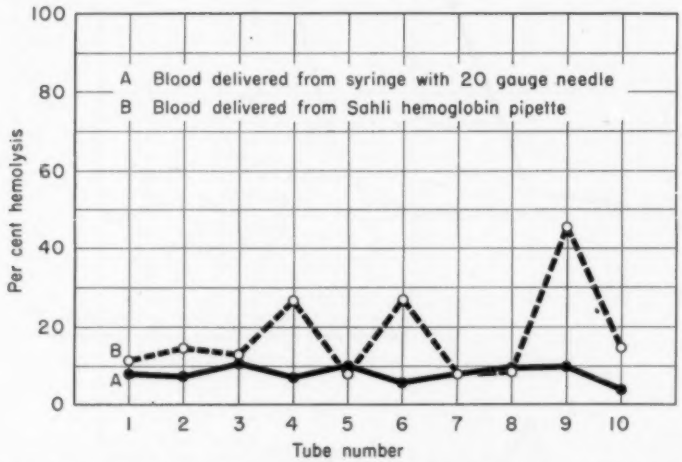

Fig. 1.—Curves showing amount of red cell hemolysis produced by the two techniques when the saline concentration of the ten tubes was kept the same (.48). Curve *A* shows the minimal hemolysis produced by delivery from a syringe with a No. 20 needle. Curve *B* shows the increased hemolysis produced by reintroducing the Sahli pipette into the specimen bottle for each tube according to the method of Suess.[6]

2. The percentage of blood hemolyzed in each tube was calculated by dividing the hemoglobin reading in grams into the 0 tube by the hemoglobin reading in grams in each tube.

3. The hemolytic increment was obtained by subtracting the percentage of blood hemolyzed in the first tube from that of the second, the second from the third, etc.

Using such a technique and plotting in such a manner, values obtained on the blood from a normal person and from a patient with familial hemolytic anemia can be seen in Fig. 2.

RESULTS

As can be seen in Table I, the blood from most of the children with cyanotic congenital heart disease had only slightly greater fragility than the normal control patients. The blood from one patient, P. A., however, did have a marked increase in fragility, as seen in Fig. 3. There was also some suggestion in this patient of spheroidocytes in her peripheral blood smear.

Oxygenating the blood had little or no effect on the fragility of the cells

from cyanotic patients. In most instances the fragility still remained slightly greater than the normal controls. Some of the blood from these newborn infants did exhibit a slight increase in fragility but others did not. Certainly none of the blood specimens were as

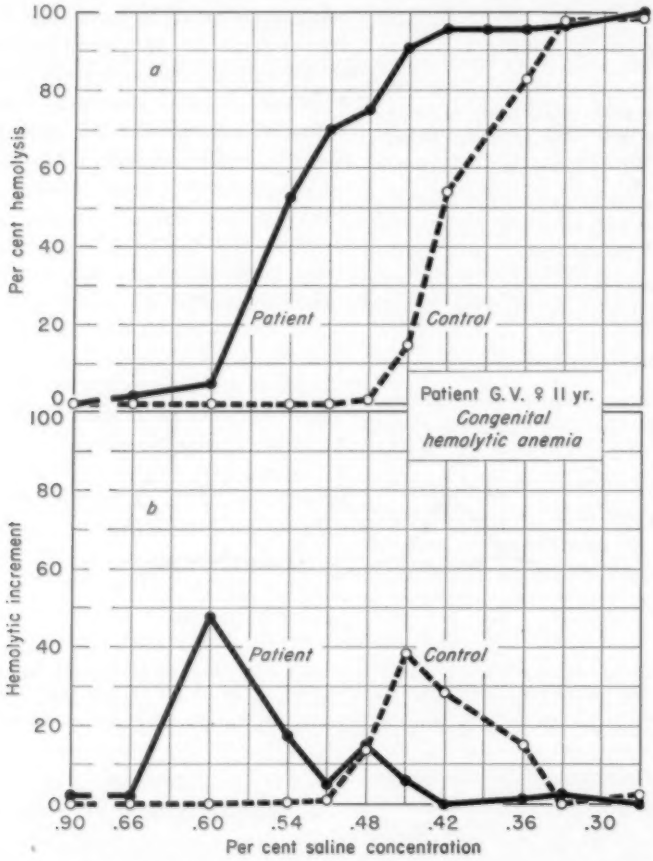

Fig. 2.—Curves obtained on blood from a patient with congenital hemolytic anemia and from a normal control patient, illustrating results plotted as (*a*) per cent hemolysis, and as (*b*) hemolytic increment according to the method of Suess.[6] Note the marked difference between the patient and the normal control patient.

In order to compare the above observations on the blood from children with cyanotic congenital heart disease with fetal blood, the cord blood from newborn infants was tested in a similar manner. Table II shows the results on ten consecutive determinations. fragile as those reported by Goldbloom.[4] Because we were unable to repeat Goldbloom's observations in this regard, we decided to determine, as he had done, the rate of spontaneous hemolysis. Goldbloom reported this to be markedly increased: e.g., after 96

TABLE I

PATIENT	AGE (YR.)	DIAGNOSIS	PATIENT		CONTROL	
			STARTED	COMPLETE	STARTED	COMPLETE
B. N.	5	Tetrad	0.6	—	.54	—
P. A.	1	NFRV*	0.9	—	.54	—
V. L.	12	Tetrad	0.6	.36	.54	.36
D. R.	2	Tetrad	0.6	.27	.54	.27
M. B.	6	Tetrad	.51	.33	.48	.36
J. R.	5	Tetrad	.51	.27	.51	.36
L. M.	11	P.S. & IAD	.51	.33	.51	.27
L. E.	2	Eisenmenger	.66	—	.54	.27
W. P.	5	Tetrad	.66	.33	.60	.36
C. S.	12	Truncus	.60	.27	.60	.27
J. F.	4	Tetrad	.66	.27	.60	.36
K. B.	5	Tetrad	.60	.33	.60	.33
L. R.	8	Truncus	.54	.33	.51	.33
J. W.	4	Eisenmenger	.54	—	.54	—
G. A.	10	P.S. & IAD	.66	.36	.54	.36
J. F.	8	Tetrad	.66	.36	.66	.33
D. L.	4	Tetrad	.66	—	.60	.27
S. H.	4	Tetrad	.66	.33	.60	—
C. M.	14	Eisenmenger	.66	.36	.60	.36
C. T.	4	Tetrad	.54	—	.45	.33
J. S.	8	P.S. & IAD	.51	—	.51	.27
D. A.	2	Tetrad	.51	.33	.51	.27
J. K.	7	Truncus	.66	—	.51	—
M. W.	14	Tetrad	.66	—	.45	.27
D. D.	13	Tetrad	.51	—	.45	—
D. C.	6	P.S. & IAD	.45	—	.45	—
K. H.	4	Tetrad	.60	.27	.45	.27

*Nonfunctioning right ventricle.
— Hemolysis not complete in lowest saline dilution used (.27).

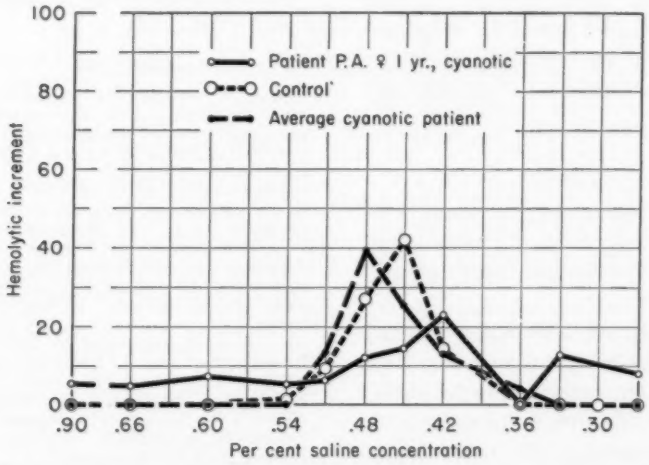

Fig. 3.—Curves obtained on the blood from the cyanotic child (P.A.) with the greatest hemolysis, from the average cyanotic child, and from the normal control patient plotted as hemolytic increments.

TABLE II

NEWBORN INFANT	NEWBORN		CONTROL	
	STARTED	COMPLETE	STARTED	COMPLETE
Baby M.	.60	.27	.54	—
Baby L.	.54	—	.54	—
Baby B.	.60	—	.51	—
Baby P.	.51	—	.51	—
Baby E.	.54	—	.54	.27
Baby O.	.54	.27	.54	.27
Baby S.	.60	.27	.60	.27
Baby C.	.60	.33	.60	.27
Baby F.	.60	.36	.60	.27
Baby E.	.60	.27	.60	.27

TABLE III

NEWBORN INFANT	CORD BLOOD	24 HOURS	48 HOURS	96 HOURS	COMMENT
Baby S.	3,840,000	3,510,000	3,850,000	3,360,000	
Baby J.	4,310,000	—	4,340,000	3,620,000	
Baby B.	5,380,000	5,640,000	—	4,960,000	
Baby H.	4,710,000	—	4,530,000	3,380,000	Single oxalate
Baby C.	4,970,000	—	—	4,040,000	
Baby D.	4,500,000	4,190,000	—	4,240,000	
Baby B.	4,990,000	4,990,000	5,070,000	4,480,000	
Baby E.	4,270,000	4,670,000	—	4,070,000	
Baby S.	4,480,000	4,600,000	—	4,640,000	
Baby W.	4,330,000	4,150,000	—	4,290,000	
Baby F.	3,600,000	3,800,000	—	3,010,000	
Baby C.	4,640,000	4,780,000	—	4,040,000	
Baby A.	4,610,000	—	4,700,000	4,220,000	

hours few or no cells remained in the oxalated cord blood specimen. As seen in Table III, we found an occasional decrease in the red cell count by ninety-six hours, but this was not marked.

SUMMARY

1. Observations on the fragility of fetal and cyanotic heart disease blood using the spectrophotometric method are reported.

2. A slight increase in the fragility of the cyanotic heart disease blood was observed. Oxygenating the blood had little or no effect on the fragility.

3. An occasional fetal blood sample exhibited a slight increase in the fragility but this was not as marked as reported by others.

4. We were unable to demonstrate a marked spontaneous hemolysis of oxalated fetal blood.

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ICTERUS PRECOX

Further Studies on Its Frequency, Etiology, Prognosis and the Blood Chemistry of the Cord Blood

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IN 1944, we described[1] the clinical syndrome of a mild form of the hemolytic disease of newborn babies, characterized by an especially intense icterus which appeared during the first twenty-four hours after birth. We called it "icterus precox" in order to distinguish it from the grave form of the same disease, icterus gravis. The existence of the syndrome was confirmed and the name suggested by us was accepted by most observers.[2, 3, 4, 5, 6, 7, 8] There is very little to add to the original clinical description of this syndrome as published in 1944.

The purpose of this paper is to report our clinical experiences with regard to the etiology, prognosis in future pregnancies, and the mental development of ninety babies who developed icterus precox, and the results of our studies of the blood chemistry of the cord blood of some of these babies.

ETIOLOGY

About 95 per cent of the first group of sixty cases of icterus precox reported by us belonged to heterospecific pregnancies (incompatibility of the blood-grouping system ABO between mother and child). In a second series of thirty additional cases we found two that were not caused by a heterospecific pregnancy but by an iso-immunization of the mother against the Rh factor of the baby. In both cases the mother as well as the baby belonged to the same blood group of the ABO system. However, both mothers were Rh negative and both babies were Rh positive. In the blood of both mothers Rh-blocking antibodies were found.

Table I

	ABO INCOMPATIBILITY				RH INCOMPATIBILITY	NO INCOMPATIBILITY
Mother	O	O	A	B	Rh Negative	A
Infant	A	B	B	A	Rh Positive	O
No cases	66	15	2	2	2	3

FREQUENCY

Among approximately 16,000 babies delivered we have found to date 90 cases of icterus precox, which gives an incidence of one case of icterus precox in 180 births. The number of heterospecific cases among the same number of deliveries was 1,250, which gives an incidence of one case of icterus precox in 25 heterospecific pregnancies.

ICTERUS PRECOX IN PRIMIGRAVIDAS

In contrast to erythroblastosis fetalis, icterus precox occurs frequently

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in first pregnancies. Of our 90 cases, 30 were first babies.

HEMOLYTIC DISEASES IN THE SIBLINGS OF SUBSEQUENT PREGNANCIES

In only a relatively small number of cases could information be obtained about the fate of children born subsequently to the babies with icterus precox. The following case, observed by us, of a family whose first child had icterus precox, while the second child died of kernicterus five days after birth, is instructive.

Mrs. M. N., 29 years old, blood group O-Rh negative. The husband was A-Rh positive. The first pregnancy terminated in an abortion in the fourth month. The second pregnancy terminated in a nonviable baby at the end of the sixth month. The third pregnancy, two years later, was brought to an end by delivery of a baby weighing 3,100 grams, which showed an intensive icterus the first day of life. The child's blood group was A-Rh positive. No hepatosplenomegaly was present and, no nucleated red blood corpuscles were found in the peripheral blood. Hemoglobin was 90 per cent, erythrocytes 3,900,000. Diagnosis: icterus precox.

This baby left the hospital on the ninth day in good general condition without need of any special treatment. He has been developing since (three years) into a physically and mentally normal child.

The fourth pregnancy started fifteen months after the birth of the first viable child. Beginning with the third month of pregnancy, we examined monthly the iso-antibodies (anti-A, anti-B, anti-Rh) in the blood of the prospective mother. At the beginning of the sixth month an increased titer of the anti-A, also of the anti-B but to a lesser degree, was noted. At the end of the pregnancy the titers of the iso-antibodies were as follows:

Anti-A agglutinins (dilution with saline)	1:128
Anti-A conglutinins (dilution with plasma)	1:1,024
Anti-B agglutinins	1:64
Anti-B conglutinins	1:512
Rh-antibodies	0

The increase of the anti-A conglutinins at the end of the pregnancy led to the prediction that the expected baby would suffer from a hemolytic disease. We expected to find an icterus precox in view of the increased anti-A-B conglutinins and the complete absence of Rh antibodies in the mother's blood. The woman was delivered at term of a male baby weighing 3,200 grams who showed, on the first day of life, an icterus which became more and more intensive. The peripheral blood had only a few erythroblasts. Hemoglobin was 90 per cent, red blood cells 4,000,000. Hepatosplenomegaly was pronounced. The general condition at the start was satisfactory but became worse on the fourth day, and the baby expired on the fifth day. Autopsy proved the case to be one of kernicterus.

This case, as well as the report by Broncato,[9] of icterus precox and erythroblastosis fetalis in two children of the same family, permits some conclusions concerning the relationship between icterus precox and the other forms of hemolytic disease of the newborn, namely, that (1) icterus precox is only a mild form of hemolytic disease of the newborn. It may occur alternately in a more severe form of the disease in different children of the same family. (2) The possibility that after an icterus precox a more severe form of hemolytic disease may occur in the same family makes it imperative to investigate systematically and repeatedly the iso-antibodies in the mother in all pregnancies subsequent to an icterus precox in order to be able to foretell an eventual occurrence of a hemolytic disease in subsequent children.

It should be emphasized, however, that neither the titer nor the kind of antibodies (anti-A, anti-B, or anti-Rh) is capable of giving us a definite clue as to the intensity of the expected hemolytic disease in that baby.

HEMOLYTIC DISEASE IN SIBLINGS PRECEDING THE ICTERUS PRECOX

In two cases there were stillbirths preceding the icterus precox. We were not able to establish definitely the cause of the stillbirths. In three more cases in which we observed an icterus precox, each time in the third child, the mothers volunteered the information that the first babies also showed an intensive icterus the first day after birth. It is possible, therefore, that the first children of these three families had icterus precox. The repeated occurrence of icterus precox in the same family as well as the occurrence of icterus precox after one of the more severe forms of hemolytic disease (icterus gravis, hydrops) should be taken into account when considering the indication of the preventive exchange transfusion.

CORD BLOOD CHEMISTRY IN ICTERUS PRECOX

The cord blood chemistry of twelve babies suffering from icterus precox was studied. These investigations seem to allow us to draw some conclusions as to the hepatic function of these babies. Of particular interest is a comparison of these results with those obtained by examining the blood chemistry of nonicteric babies as published in a previous article.[10]

As can be seen in Tables II and III, the studies did not show any significant differences between icteric and nonicteric babies, with the exception of a particularly high bilirubin content in the blood of the icterus precox babies. In all but one case the bilirubin content was over 1 mg. per cent, and in nine of the twelve cases the direct van den Bergh test was positive.

The average value of *total bilirubin* in the serum of the cord blood was 3.57 mg. per cent for the icterus precox in contrast to a total of 0.94 to 1.34 mg. per cent in various groups of nonicteric babies (premature, full term and postmature).

The *total cholesterin* in the serum of the cord blood showed an average of 88.4 mg. per cent which is about 20 mg. per cent less than in normal full term, and 3.7 mg. per cent more than in postmature nonicteric babies.

The *total protein* was 5.57 Gm. and the *albumin-globulin ratio* showed an average of 1.78 which is about what we found in nonicteric babies.

The *cephalin-cholesterol flocculation test* was positive in nine of the twelve cases (mostly 4 plus).

The *thymol turbidity test* showed low values in all twelve cases of icterus precox similar to the findings in normal newborn infants (average 1.6 U.).

In all cases of icterus precox a mild left deviation of the *Weltman coagulation band* occurred.

Thus chemistry of the cord blood of newborn babies with the icterus precox syndrome does not differ substantially from that of nonicteric babies, with the exception of an elevated bilirubin content in the blood of icteric newborn infants.

PROGNOSIS

The immediate prognosis in the case of the newborn baby suffering from icterus precox is always good. These babies need no special treatment, and

TABLE II

	AVERAGE VALUES			
	BILIRUBIN MG. PER 100 C.C.	TOTAL CHOLESTEROL MG. PER 100 C.C.	TOTAL PROTEINS GM. PER 100 C.C.	ALBUMIN-GLOBULIN RATIO
Nonicteric infants				
Premature	0.94	95.1	5.36	2.52
Full term	1.16	108.3	5.70	1.61
Postmature	1.34	84.7	5.57	1.62
Icterus precox	3.57	88.4	5.57	1.78

TABLE III

	BILIRUBIN MG. PER 100 C.C.			PROTEINS GM. PER 100 C.C.				TESTS				
CASES	TOTAL	DIRECT	INDIRECT	CHOLESTEROL (TOTAL) MG. PER 100 C.C.	TOTAL	ALBUMIN	GLOBULIN	ALBUMIN-GLOBULIN RATIO	CEPHALIN FLOCCULATION	TAKATA-ARA	WELTMAN COAGULATION	THYMOL TURBIDITY	CADMIUM SULFATE
1	0.8	Neg.	0.8	--	5.50	3.50	2.00	1.75	++++	Neg.	6	1 U.	Neg.
2	1.5	1.0	0.5	90	5.50	3.80	1.70	2.23	Neg.	Neg.	6	--	--
3	1.4	9.0	0.5	78	5.65	3.55	2.10	1.66	Neg.	Neg.	6	3-4 U.	Neg.
4	1.0	Neg.	1.0	92	5.60	3.60	2.00	1.80	Neg.	Neg.	6	1-2 U.	Pos.
5	7.0	2.3	5.2	104	6.60	4.10	2.50	1.48	++++	Neg.	7	2-3 U.	Neg.
6	1.0	Neg.	1.0	99	5.40	3.30	2.10	1.55	++++	Neg.	7	2 U.	Neg.
7	5.5	3.0	2.5	92	4.95	3.30	1.65	2.00	++++	Neg.	6	2 U.	Neg.
8	4.5	3.0	1.5	113	5.70	4.00	1.70	2.35	++++	Neg.	7	1-2 U.	Neg.
9	5.6	1.0	4.6	64	5.70	3.50	2.20	1.62	++++	Neg.	7	0-1 U.	Neg.
10	5.8	0.7	5.1	79	5.50	3.40	2.10	1.60	++++	Neg.	7	2 U.	Neg.
11	3.5	0.5	3.0	75	5.20	3.10	2.10	1.47	++++	Neg.	8	1 U.	Neg.
12	2.8	0.9	1.9	86	5.50	3.20	2.30	1.39	++++	Neg.	8	1 U.	Neg.

they develop without particular difficulties in spite of the mild anemia present at birth and which may even increase during the following weeks and months.

The future prognosis of icterus precox is favorable, in contrast to that of icterus gravis. In 10 patients with icterus precox observed up to the third year of life we could detect no sign of mental deficiency nor of neurologic symptoms, as are so often seen in babies surviving icterus gravis.

DISCUSSION

Icterus precox is a mild form of hemolytic disease of the newborn. It was, until recently, and is sometimes even today, frequently mistaken for either the physiologic icterus or the icterus gravis.

The occurrence of icterus precox and one of the more severe forms of hemolytic disease of the newborn in the same family based upon the same etiological factor permits the conclusion that we are dealing, not with a disease different from the other forms of the same syndrome, but, for reasons yet unknown, one child is afflicted with a mild form and another child of the same family is afflicted with a severe form of the same disease.

We have not been able to detect a special order or serial regularity in which the various forms of hemolytic

disease occur in the same family. In only one instance kernicterus followed icterus precox in the same family. In two cases we had reason to assume that severe erythroblastosis (hydrops) preceded the icterus precox, and in three cases icterus probably occurred twice in the same family. The marked frequency of occurrence of icterus precox in heterospecific pregnancies (AB incompatibilities) and its relative rarity in cases of Rh incompatibility seems to point toward a certain connection between the etiology of icterus precox and the anti-A and anti-B antibodies. However, we cannot accept the explanation suggested by Wiener that the cause of the milder form of hemolytic disease in cases of ABO incompatibilities is due to a selective permeability of the placenta for the Rh-blocking antibodies and a relative impermeability for the anti-A-B agglutinins, for the following reasons:

1. In 40 per cent of all newborn babies anti-A-B agglutinins and conglutinins were found in the cord blood that disappeared from the peripheral blood of the newborn infant by the eighth day. They must have, therefore, originated in the blood of the mother.

2. The iso-immunization of the mother caused by the A or B agglutinogen of the child not only produces an increase in the anti-A-B agglutinins but also causes the appearance of anti-A-B immuno-iso-antibodies (conglutinins) which can be seen only in a dilution with plasma or protein—as is the case with the Rh-blocking antibodies—and therefore is bound to have passed the placenta as the latter does.

3. Icterus precox occurs not less frequently than the other forms of hemolytic disease, and it occurs in the same proportion of one in twenty-five to thirty heterospecific pregnancies, corresponding to one erythroblastosis fetalis in twenty-five to thirty cases of Rh incompatibilities. We are of the opinion, therefore, that we are not dealing with a rarer form as would be expected according to Wiener's theory of *selective permeability* of the placenta but only with an attenuation of symptoms of the hemolytic diseases of newborn infants, for reasons as yet unknown.

Neither is the theory of the *competition of antigens* as an explanation for the occurrence of icterus precox applicable in all cases. In two of the cases observed by us in which there was an Rh incompatibility, both mother and child belonged to the same group of the ABO system.

In conclusion, we still do not have a plausible explanation of the fact that in certain cases of incompatibility of blood groups between mother and child, icterus precox develops.

SUMMARY

1. To date, we have diagnosed ninety cases of icterus precox among 16,000 births. Almost all of them were caused by an autoimmunization of the mother through the antigen A, B of the children. Only two cases were due to an Rh incompatibility.

2. The blood chemistry of the cord blood in these cases is not materially different from that in nonicteric children.

3. The immediate and future prognosis of the children suffering from icterus precox is favorable.

4. The occurrence of icterus gravis (kernicterus) after icterus precox in the same family makes special attention and precaution imperative in

pregnancies following one in which icterus precox was present.

5. The theories of competition of antigens, and of selective permeability of the placenta to various isoantibodies, do not satisfactorily explain the occurrence of icterus precox in certain cases of isoimmunization of the mother against the blood group antigen of her child.

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PURULENT AND SEROUS SUBDURAL EFFUSIONS IN THE COURSE OF PURULENT MENINGITIS

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THE sequelae of the purulent meningitides have become increasingly important as the survival rate has been increased through use of better chemotherapeutic and antibiotic agents. Simple survival is no longer a feat, but the survival of a patient with normal capacities and potentialities has now become a paramount necessity. Early diagnosis and adequate treatment is still the order of the day, but where this is accomplished, complications bearing on the ultimate normality of the patient must be watched for. It has recently become evident that one of these complications can be diagnosed and treated in a satisfactory manner. This interesting, and as yet unelucidated, phenomenon is focal subdural effusion, first described by McKay and associates,[1] while Smith and collaborators[2] made similar independent observations.

Historically, this condition has been recognized infrequently. An effusion into the subdural space as a complication of diseased sinuses, or mastoids, was noted as early as 1923 by Penfield.[3] In 1945, two autopsy cases were reported by Spitz and co-workers,[4] in which subdural exudation followed a purulent meningitis, one being due to a type VIII pneumococcus, and the other to an *Hemophilus influenzae*. In these two cases no extension from a focus in the adjacent respiratory system could be found. In January of 1950, McKay and associates[1] of Boston, reported on nine cases of subdural effusion complicating type B *H. influenzae* meningitis, and Smith and collaborators,[2] in New Orleans, extensively studied twenty cases of subdural effusion, and described this complication thoroughly.

It is the purpose of this report to describe four cases of subdural effusion. In view of the limited number of reports of this secondary lesion of purulent meningitis, it was considered worth while to report these four cases, particularly in view of the fact that two of these showed clinical findings not previously reported.

PRESENTATION OF CASES

Four cases are presented, all seen at The Children's Memorial Hospital, Montreal, in the last six months of 1950.

CASE 1.—P. R., a 3½-month-old white male, weighing 5 kilograms, entered the hospital with a three-day history of vomiting, refusal of food, irritability, and a temperature of 104° F., having had a generalized convulsive seizure, lasting fifteen minutes, on the day of admission.

On admission, he was an acutely ill, dehydrated, stuporous, febrile infant, who had a very stiff neck, a full anterior fontanel, and a positive Brudzinski sign.

Laboratory data: The white count was 12,600 per cubic millimeter of which 6,000 were polymorphonuclears,

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and the hemoglobin was 9.0 Gm. Cerebrospinal fluid showed over 600 cells, with 80 per cent polymorphonuclears, a strongly positive Pandy, sugar 20 mg. per 100 c.c., and protein 397 mg. per 100 c.c. The smear showed gram-positive diplococci, and spinal fluid culture grew *Diplococcus pneumoniae*. Blood culture was sterile.

The infant was treated with large, frequent doses of crystalline penicillin parenterally, and was also given sulfadiazine at 150 mg. per kilogram per twenty-four hours, as well as appropriate intravenous fluid therapy. His course in the first forty-eight hours was characterized by convulsive movements, twitchings, and continuous fever. Aureomycin 50 mg. per kilogram was also given. By the fifth hospital day, the baby was eating well, had no convulsions, but was showing a low-grade fever, with stiffness of all extremities. On the tenth hospital day, because of the continued spasticity and a full fontanel, bilateral subdural taps were done through the fontanel, and on the right side there were found 2 c.c. of lemon yellow fluid. Four days later, the subdural fluid was demonstrable bilaterally, and 3 to 8 c.c. were removed every second day. On the fourteenth day, lumbar cerebrospinal fluid was clear, showed 8 white cells, negative Pandy, sugar 40 mg. per 100 c.c., and protein 36.3 mg. per 100 c.c. In contrast, the subdural fluid was yellow and had a protein content of 1,500 mg. per 100 c.c. Subdural taps were lengthened to weekly, and by the twenty-fifth hospital day, the left side showed no fluid, and the baby was greatly improved. The right side still showed a small effusion. On the fiftieth hospital day, the infant was discharged, to return in ten days for re-examination.

At this visit, the mother complained of the baby's irritability, but he was doing well otherwise. Subdural taps were repeated and were negative. A developmental evaluation showed retardation in physical, social, and adaptive behavior. When seen two weeks later, irritability was decreased, and at another visit six weeks after discharge from hospital, he was a healthy 6-month-old infant, who showed normal behavior for his age.

CASE 2.—J. C., a 2-month-old white female, weighing 3.4 kilograms, entered the hospital with a history of irritability for forty-eight hours previous to admission, unwillingness to eat for eighteen hours, and twitching of the left side of the face, left arm, and left leg on two occasions in the twelve hours before admission.

On admission, the baby was small but well nourished, listless, had a whimpering cry, and was very irritable when disturbed. Examination showed a full and tense anterior fontanel, a moderately stiff neck, a positive Brudzinski sign, and a purulent otitis media.

Laboratory data: The white count was 7,000 per cubic millimeter of which 5,100 were polymorphonuclears. The hemoglobin was 10.1 Gm. Cerebrospinal fluid showed over 900 cells of which 76 per cent were polymorphonuclears, a 2+ Pandy, and the smear showed gram-positive diplococci. Culture yielded a heavy growth of *D. pneumoniae*. The blood culture was sterile.

The baby was treated with large, frequent doses of parenteral crystalline penicillin, and sulfadiazine, 100 mg. per kilogram per twenty-four hours. On the second hospital day, an area of erythema, edema, and local heat was noted which extended 2 cm. beyond the margins of the anterior fontanel, and was visible in the midline on the upper forehead. The fontanel was very tense and bulging. Spinal fluid culture was sterile on this day. On the third hospital day, left-sided motor seizures of the arm and leg were noted, the tenseness of the fontanel was not relieved by lumbar puncture, and the erythema was still present. Subdural taps were done bilaterally, and from the right side 6 c.c. of cloudy, yellow, purulent material were removed, which showed 2,500 mg. protein per 100 c.c., culture yielded

D. pneumoniae, and the fluid was demonstrated by the bacteriologist to contain penicillin, which, by a rough qualitative test, adequately *inhibited a culture of D. pneumoniae.* From the left side 1 c.c. of a lighter yellow fluid was obtained, which was sterile. Twenty-four hours after the removal of the purulent effusion from the right, the area of edema, erythema, and local heat had disappeared. On the sixth hospital day, subdural taps were dry. Left-sided motor seizures occurred until the tenth hospital day, one to two per day, and none after that. The baby was discharged on the twenty-second hospital day to be seen in two weeks. An electroencephalogram done on the twentieth hospital day was interpreted as follows:

"There was a slight but persistent asymmetry of background activity over the centroparietal regions, that on the right being of lower voltage. The record was fairly stable throughout for an infant. There was no clear evidence of a focal or diffuse epileptogenic process or of severe cerebral lesion. The depression of voltage would probably be accounted for by the subdural effusion."

Thirty-six days after admission, at the age of 3 months, the baby weighed 4.5 kilograms, and the fontanel was open 3 fingerbreadths and soft. Development evaluation showed normal 12 weeks' behavior. At the age of 5 months she weighed 6.7 kilograms, was regarded as normal developmentally, and had had no further convulsions.

CASE 3.—R. L., an 11-month-old white male, entered the hospital with a history of nasal discharge for a week, vomiting, pallor, apathy, drowsiness, hard breathing for two days, and a slight cough for one day. The child was acutely ill, with rapid breathing, irritability, and pallor. Physical examination showed forceful pulsation in a small anterior fontanel, a very stiff neck, and moderate dehydration.

Laboratory data: The white count was 8,300 per cubic millimeter of which 7,000 were polymorphonuclears, and the hemoglobin was 9.6 Gm. Spinal fluid showed over 10,000 cells, with 97 per cent polymorphonuclears, a strongly positive Pandy, protein 103 mg. per 100 c.c., sugar 32.8 mg. per 100 c.c. The smear showed gram-negative pleomorphic rods, and a culture of the fluid yielded *H. influenzae,* type B. Blood culture also grew *H. influenzae,* type B.

The baby was treated with oral chloramphenicol at 100 mg. per kilogram as a loading dose, and 250 mg. were given every eight hours,[5] for one week. Twelve hours after institution of chloramphenicol a lumbar puncture was done, and the spinal fluid showed no growth. On the fourth hospital day, the child still had a temperature of 101° to 102° F., and in general did not seem to be doing well. Bilateral subdural taps were done, and from the right only were obtained 3 c.c. of lemon yellow translucent fluid which showed about 300 white cells, and one drop of this solidified in Pandy's solution. Following the subdural taps, the temperature fell to normal abruptly and showed no further rises. Repeat subdural examinations on the eighth day were negative. The spinal fluid on the thirteenth hospital day showed 47 mononuclears and 14 polymorphonuclears and a protein content of 62.7 mg. per 100 c.c. The child was discharged on the fourteenth hospital day. He was seen at one year of age, at which time his head measured 47.5 cm., crown-heel length was 76.5 cm., weight 12.5 kilograms. Examination revealed no pertinent positive findings, and on developmental testing, he functioned at a one-year level in all fields.

CASE 4.—M. L., a 4-month-old white male, was brought into the hospital with an eight-day history of fever, anorexia, drowsiness, and pallor and convulsions in the three days preceding admission. The convulsions were characterized by generalized seizures, with fixation of the eyes, but without cyanosis, lasting ten to fifteen seconds. Six such attacks occurred previous to

admission. A visiting physician gave one injection of penicillin twenty-four hours before admission.

Physical examination revealed an acutely ill, malnourished infant. The fontanel bulged 0.5 cm. above the expected cranial contour, and measured 5 × 7 cm. It did not pulsate. The skin over the fontanel was markedly erythematous, hot and tense, slightly more so on the right side. The head measured 39 cm. The extremities were tense, hands fisted, and the Brudzinski sign was positive.

Laboratory data: The white blood count was 7,800 per cubic millimeter, of which 4,680 were polymorphonuclears, and the hemoglobin was 8.3 Gm. Spinal fluid showed 2,100 cells, mostly polymorphonuclears (1,800), and a 4+ reaction with Pandy's solution. The spinal fluid sugar was 13 mg. per 100 c.c., the protein 293 mg. per 100 c.c. Smear and culture showed *D. pneumoniae*. The blood culture was negative.

Shortly after admission, bilateral subdural taps were done. From the right subdural space were obtained 2 c.c. of yellow, very cloudy fluid, one drop of which solidified in Pandy's solution, and from the left were obtained 5 c.c. of cloudy yellow fluid, of similarly high protein content. Smears from both sides showed gram-positive Diplococci, which on culture were *D. pneumoniae*. Twenty-four hours later, the right subdural tap was negative, and remained so, while on the left there were 2 c.c. of cloudy yellow fluid which cleared by the fourth tap and remained dry. Twenty-four hours after the original subdural tap, the fontanel was much less tense, the erythema had decreased and was visible only on the right, from which side the more purulent material had been obtained. On the third hospital day, the baby showed generalized spasticity, with generalized convulsions, necessitating sedation. On the fifth hospital day, he was taking oral feedings, was less spastic, and only occasional twitchings were seen. The spinal fluid was now clear, showed 65 cells, with 70 per cent lymphocytes, and a positive Pandy. Supportive transfusions were given. By the tenth hospital day, edema was prominent, and both kidneys were greatly enlarged.

Total blood protein was then 4.94 Gm., albumin 2.99 Gm., globulin 1.95 Gm., albumin-globulin ratio 1.53, nonprotein nitrogen 70.8 mg. per 100 c.c. The urine showed a specific gravity of 1.004, no albumin, no sugar, 4 to 6 red cells and an occasional white cell per high-power field. The kidneys gradually decreased in size, the edema cleared, and the nonprotein nitrogen returned to normal. However, the picture of spasticity, occasional tonic and clonic convulsions, and mental retardation persisted. Injection of 40 per cent Diodrast into the superior longitudinal sinus, through the fontanel, showing no filling of the left lateral or sigmoid sinuses, but a good flow was present into the right lateral, sigmoid, petrosal, and jugular sinuses. A pneumoencephalogram showed marked dilatation of the lateral ventricles, and was compatible with a communicating hydrocephalus. An intravenous pyelogram showed a normal-appearing right kidney; the left was not visualized.

Four months after the original illness, the patient showed marked spasticity of the extremities, developmental retardation, and frequent generalized convulsions, which were not entirely controlled by sedation.

DISCUSSION

The finding of subdural effusions in the course of purulent meningitis is common, as judged from the available literature, from which it appears that the incidence may be as high as 50 per cent.[1, 2] Effusions have been reported to be common in pneumococcus and in *H. influenzae* meningitis, rare in meningococcus meningitis, and we

have seen one small serous effusion in the course of a beta-hemolytic streptococcus meningitis. The true incidence of this complication will become obvious only after large numbers of children are examined for this condition.

The indications for subdural taps in a child with purulent meningitis may be enumerated:

1. A bulging fontanel which is not relieved by lumbar puncture.

2. Failure to make good clinical response in forty-eight to seventy-two hours of therapy usually adequate for the type of meningitis. A child may show persistence of fever, vomiting, and convulsions, or the physician may have the clinical impression that the child is not doing well.

3. Presence of an area of erythema, edema, and local heat involving the region of the anterior fontanel. In two of the cases described, this sign was present, and was found to indicate a purulent subdural effusion (Cases 2 and 4).

4. Focal convulsions at any time in the course of meningitis.

5. Generalized convulsions after an initially good clinical and febrile response to therapy.

6. Persistent vomiting after good initial response to therapy.

7. Disturbance in auditory acuity or changes in the optic discs in the course of meningitis.

Examination of the subdural space is mandatory, we believe, in all infants with an acute purulent meningitis who have an open fontanel or cranial sutures which allow entry of a needle. This should be done between the fifth and seventh day of disease, unless one of the indications for subdural examination arises earlier. In this case, immediate examination is important. In older children with closed fontanels, one might investigate the subdural space through burr holes, when any of the above indications is present.

The character of the effusion seems to fall into two general groups: the serous type (the more common), and the purulent type. Both types of effusion may cause severe symptoms.

	SEROUS	PURULENT
Color	Yellow—Clear	Yellow—Cloudy
Cells	Low—RBC and WBC	High—pus cells
Bacteria	Culture negative	Culture positive
Pandy	Very positive	Very positive
Protein	0.5-2.5 Gm. per 100 c.c.	0.5-2.5 Gm. per 100 c.c.

The therapy of this condition varies. After a diagnosis of subdural effusion is made, subdural taps should be repeated every forty-eight hours. One may find that by the second or third tap, fluid can no longer be obtained (Case 3). Subdural needling may then be discontinued unless indications arise. If examinations, done every second day, continue to show subdural fluid for ten to fourteen days, one may then lengthen the interval to one week, and find that the effusion will clear (Case 2). If large amounts of subdural fluid continue to form, craniotomy and search for a subdural membrane are indicated.[1, 2]

When subdural effusions were first described, many felt that the incidence of severely brain-damaged children could be markedly reduced by diagnosing this condition, and treating it. Certainly in the first three of the four cases described here, the end result, without relief of the subdural effusions, would have been poor, probably with convulsive disorders, spasticity, and mental deterioration. The out-

come in the fourth child (Case 4), in whom the prognosis could only be described as poor, emphasizes the fact that long-standing untreated meningitis may cause very diffuse brain damage, hydrocephalus, and focal necrosis. Early diagnosis with relief of subdural effusion does appear to markedly reduce some of the serious sequelae of purulent meningitis, although the well-known complications of meningitis may still occur. It must also be noted that focal effusions may be present in subdural areas not easily accessible to a needle at the usual site of the tap.

SUMMARY

1. Four cases of subdural effusions complicating purulent meningitis are presented in detail.

2. The finding of an area of erythema, edema, and local heat involving the region of the anterior fontanel was indicative of a purulent subdural effusion in two cases, and has not previously been reported.

3. Indications for subdural exploration are enumerated.

4. There is evidence in three of the patients that repeated aspirations of the accessible subdural effusions prevented the development of sequelae of purulent meningitis, at least for the period of their follow-up, nine months.

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A PRELIMINARY REPORT OF THE USE OF A NEW PLASTIC INTUBATION TUBE

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MAINTAINING nutrition in patients in coma, with marked debility, or with cleft lip and palate is a major problem. However, with the advent of a new plastic feeding intubation tube, this appears to be minimized, and the trauma inflicted upon the esophagus and nasopharynx by gavage feeding is obviated.

A radiopaque plastic tube, with the trade name of Plexitron,* was used in this study. It is 38 inches long with an internal diameter comparable to a size 8 French catheter. The tube's flexibility can be regulated by warming or chilling. They are individually packaged, and are clean, ready to use. No heating or sterilization is necessary. However, they can only be used once, and must not be cleaned and re-used.

We have used these tubes in the cases noted in Table I. In two patients, Cases 14 and 24, it was used as a substitute for a Levine tube in establishing Wangensteen suction. The results were considered "excellent" if the tube was well tolerated, and adequate nutrition could be maintained. The plastic tube was unsuccessful in only two of the twenty-four cases presented. Both patients had congenital heart disease with enlargement of all chambers of the heart. In no instance was it necessary to remove the tube because of irritation to the upper respiratory passages or esophagus, or because of wear and tear on the tube. Of the twenty-two cases, the plastic tube was maintained in place on an average of thirteen days. The duration of intubation ranged from one to fifty-one days.

The following brief case report exemplifies the efficacy of the Plexitron tube.

CASE 1.—D. C., a 2-month-old white male infant, entered the hospital on Nov. 30, 1949, for repair of a cleft lip and palate. He weighed 9 pounds, 11 ounces at time of admission, and was being fed by gavage. On Dec. 23, 1949, the patient was esophagoscoped by one of us (A. H. A.), as he had been regurgitating for two weeks, and failed to respond to the usual therapeutic measures. Barium meal had been normal. Esophagoscopy revealed "inflammation in the cricopharyngeal area, plus an area of inflammation in the upper esophagus."

The patient developed diarrhea, and went downhill, necessitating intravenous fluids and blood transfusions. On December 30, the patient weighed 8 pounds, 15 ounces, at which time a Plexitron tube was inserted via the right nostril into the stomach. This tube was maintained in place until Jan. 17, 1950, when the patient had a primary closure of his harelip. At this time, the patient weighed 10 pounds. The tube was well tolerated, causing no discomfort at any time.

Following surgery, the patient was fed by eyedropper. He made an uneventful recovery, and was discharged from the hospital on January 28, weighing 10 pounds.

From the Children's Memorial Hospital.

*No. NS-300, manufactured by Baxter Laboratories, Morton Grove, Ill.

TABLE I

	PATIENT	DIAGNOSIS	DURATION OF INTUBATION (DAYS)	RESULTS	COMMENTS
1.	D. C. 2 mo.	Cleft lip and palate	17	Excellent	Uneventful recovery following surgery.
2.	B. C. 7 wk.	Congenital heart disease	5	Excellent	Removed at request of parents. 6 oz. weight gain. 23 oz. intake per day with tube as opposed to 14½ oz. intake by mouth. *Expired.* Autopsy-auriculoventricular communis defect.
3.	R. A. 11 mo.	Miliary tuberculosis and meningitis	32	Excellent	Expired. Autopsy—miliary tuberculosis and tuberculous meningitis
4.	J. W. 2½ mo.	Congenital heart disease Transposition of great vessels	Momentary	Excellent	Expired. Autopsy—transposition of the great vessels and enlargement of all heart chambers. Not tolerated because of cyanosis and apnea.
5.	S. A. 7 wk.	Multiple congenital anomalies—cleft lip and palate, hydrocephalus, and Pierre-Robins syndrome	14	Excellent	Expired. Autopsy—hydrocephalus, cleft lip, and palate.
6.	S. J. 19 da.	Postoperative tracheoesophageal fistula	18	Excellent	Uneventful recovery. Inserted because of postoperative anastomotic leak.
7.	M. McM. 8½ mo.	Encephalitis, organism unknown	14	Excellent	Home with tube in place. No follow up.
8.	J. B. 2 da.	Cleft lip and palate	31	Excellent	Fed with dropper and sustained a weight loss. Tubes well tolerated.
9.	D. E. 3 mo.	Transposition of the great vessels	Momentary	Poor	Not tolerated. Removed immediately because of cyanosis and dyspnea.
10.	D. S. 2 mo.	Cleft lip and palate	51	Excellent	Uneventful recovery following surgery.
11.	J. T. 2½ yr.	Lead poisoning and encephalitis	6	Excellent	Awakened from coma, and was able to feed.
12.	T. A. 5½ yr.	Measles, encephalitis	10	Excellent	Awakened from coma, and was able to feed.
13.	B. B. 2½ mo.	Diarrhea and malnutrition	6	Excellent	Able to feed when general condition improved.
14.	R. L. 4 da.	Imperforate anus with rectourethral fistula	2	Excellent	Used as Wangensteen suction to relieve postoperative ileus.
15.	G. A. 7 yr.	Congenital esophageal stricture	8	Excellent	Used postoperatively as Wangensteen suction to relieve postoperative ileus.
16.	T. J. 6 wk.	Postoperative imperforate anus with diarrhea and debility	5	Excellent	Nutrition improved while debilitated.

TABLE I—CONT'D

	PATIENT	DIAGNOSIS	DURATION OF INTUBATION (DAYS)	RESULTS	COMMENTS
17.	R. B. 6 wk.	Agenesis of myenteric plexus (bowel obstruction)	6	Excellent	Nutrition improved while debilitated.
18.	A. J. 14 da.	Tracheoesophageal fistula	6	Excellent	Expired. Autopsy—postoperative T-E fistula operated and duodenal atresia.
19.	D. F. 2½ yr.	Tuberculosis meningitis	15	Excellent	Expired. Autopsy—tuberculous meningitis and miliary tuberculosis.
20.	D. M. 21 mo.	Tuberculosis meningitis	17	Excellent	Expired. Autopsy—tuberculous meningitis and miliary tuberculosis.
21.	W. B. 14 da.	Cleft lip and palate	3	Excellent	Nutrition improved. Surgery performed.
22.	K. S. 1 mo.	Tetralogy of Fallot	17	Excellent	Expired. Autopsy—tetralogy of Fallot.
23.	C. W. 8 yr.	Postbulbar poliomyelitis	1	Excellent	Home with same. Developed esophagitis and pharyngitis from gavage feeding with rubber tube.
24.	C. T. 10 da.	Gastroenteritis, severe	1	Excellent	Used as Wangensteen suction. Ileus relieved. Removed after 24 hours.

Instructions for use are as follows: The plastic tube is inserted via one nostril in the same manner that a Levine tube is inserted. The excess tubing is taped to the patient's forehead, or in the case of an infant, to the head of the crib. Feedings are administered by continuous drip or on a three- to four-hour schedule. This latter method was used almost exclusively in our study. An infant's formula is placed in a 30 c.c. syringe to which is attached a 20 gauge needle that is inserted into the end of the Plexitron tube. Immediately following each feeding, using a clean syringe and needle, one ounce of cool, boiled water is instilled into the tube, thus cleansing it.

COMMENT

A new plastic feeding tube is described, and its clinical use in twenty-four cases summarized. The average duration of intubation, without removal, was thirteen days; being maintained in place for fifty-one days in one patient. It has a decided advantage over gavage feeding with a rubber tube, in that this plastic tube can be left in place for prolonged periods of time, and is atraumatic to the upper respiratory passages and esophagus.

METHODS OF SECURING UNIFORMITY IN HOSPITAL STATISTICS ON PREMATURE INFANTS IN NEW YORK CITY

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PUBLIC health workers have encountered certain difficulties and inaccuracies in attempting to measure the rate of survival of premature infants. There is still much to be done to attain uniformity in statistics on prematurity at a community level. What is not as evident is that there are as many difficulties and inaccuracies in such statistics within the individual hospital. One would expect it to be relatively easy for an individual hospital to count its premature infants accurately. Most hospitals think they do, especially those which give special care to premature infants. It is obvious that a uniform method of keeping statistics on premature infants is necessary, in order to evaluate the effectiveness of care afforded in premature centers. In this paper, we will report on a sampling analysis of such inaccuracies, and on the method developed to overcome them in special premature centers in New York City. The problem of survival among premature infants in New York City is of considerable import; well over half of all infant deaths occur in premature infants. About 8 per cent of the 150,000 live births each year in New York City are premature by birth weight definition. Whereas infant mortality in New York City is slightly less than 2.5 per cent, among premature infants it is approximately 17 per cent.

Description of the Problem.—To test the completeness of statistics on premature infants at the hospital level, a staff member from the Department of Health was assigned the work of tabulating statistics on premature infants in two of the hospitals in New York City whose care of premature infants was recognized to be good. He made a list of all infants who were born alive in these two hospitals weighing less than 5 pounds, 9 ounces (2,500 grams or less) for a period of one year, and then followed the course of such infants until they were either discharged home or died in the hospital. The initial list was made up from the hospital's own birth registry, so that there was little possibility that any infant was excluded. Each infant was followed as long as he remained in any part of the hospital and wherever he was cared for—delivery room unit, premature unit, full-term or regular newborn nursery service, suspect nursery, isolation nursery, pediatric service, or any other department of the hospital to which any infant was transferred. After tabulation, comparison was made with the hospital's own data. Wide discrepancies between the two sets of data—the Health Department's and the hospital's—were found in each hospital

From the New York City Department of Health.

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for readily ascertainable reasons. These reasons were:

1. Not all premature infants born alive in the hospital were included in the hospital's data.

a. Some premature infants who died in the delivery room without reaching any nursery were excluded from the hospital's data.

b. Some premature infants were never admitted to the premature unit, and so were omitted from the hospital's data. This group was usually the larger babies weighing 4½ to 5½ pounds at birth, and was cared for in the full-term or regular nurseries.

2. Not all premature infants born alive in the hospital were followed through until hospital discharge or death.

Some premature infants were originally cared for in the premature unit, and then, because of medical or surgical complications, were transferred to the hospital's suspect and isolation nurseries, or to the general pediatric service. Some of these babies were then tabulated as discharged alive when the actual outcome in the hospital was unknown and might have been death. In fact this group was more likely to terminate in death, since they were transferred out of the premature unit and into other services of the hospital because of the seriousness of their complication.

3. The definition of a premature infant varied from hospital to hospital.

a. In some hospitals duration of pregnancy rather than birth weight of the infant was used as the criterion of prematurity.

b. In other hospitals, the upper weight limit for a premature infant varied in a range from 4½ to 5½ pounds.

c. In some hospitals, the attending physician classified the infant as premature, basing his decision on factors other than weight or gestation.

4. In some hospitals which cared for premature infants born outside the hospital and transferred in, there was no separation of the "intramural" and "extramural" groups in the hospitals' statistical tabulations. Since the risk of dying is greater in the "extramural" group, it is not sound to analyze them together as one group.

This study and other observations therefore confirmed conclusively from a statistical point of view that the two hospitals' own tabulations were inadequate, and that there was little or no uniformity in collecting data for the computation of mortality rates among premature infants in hospitals. The following method of keeping hospital statistics on premature infants was therefore developed with the assistance of the Health Department's Pediatric Advisory Committee and of the pediatricians-in-charge of the participating premature centers.

METHOD ESTABLISHED FOR SECURING UNIFORMITY IN HOSPITAL STATISTICS ON PREMATURE INFANTS

In establishing a system of keeping uniform statistics on premature infants, certain principles must be laid down and then followed:

1. All premature infants must be included in the tabulations.

2. All premature infants must be followed through in the hospital until hospital discharge, death, or until they have reached an agreed-upon maximum weight which can for all practical purposes be taken to indicate that the infant is being kept in the hospital for reasons other than prematurity.

3. For the purpose of comparability, the "extramural" premature infants (those born outside the hospital and transferred in) must be separated from the "intramural" group, since a premature center usually attracts from other hospitals and from the home the smaller premature infant and the premature infant who is not doing well.

4. There must be a basic place or places in the hospital where all new-

born admissions are listed, that is, a hospital birth registry or a hospital delivery room book plus a transfer-in-book so that it may be possible to select all of the premature infants to be tabulated.

The method established consists essentially of four parts: (1) definition of terms; (2) records; (3) procedure of follow-up; (4) preparation and submission of periodic tabulations and reports. This material was set up in a guide and is now being put into use in the premature centers in the city.

1. *Definition of Terms.*—A premature infant is defined as any infant born alive or cared for in the hospital for prematurity whose birth weight or earliest known weight is less than 5 pounds, 9 ounces (2,500 grams or less).

The term "born alive" as defined in the New York City Sanitary Code means a "sign of life, such as respiration, heartbeat, or movement of voluntary muscle, after complete separation of the body of the child (head, trunk, and limbs) from the body of the mother, notwithstanding whether the cord was or was not cut, or the placenta was or was not removed."

Birth weight was defined for both "intramural" and "extramural" premature infants. In the case of "extramural" infants, the birth weight is the weight at birth reported by the transferring hospital. In the case of "intramural" infants, the birth weight is the weight in the delivery room. If the infant is not weighed in the delivery room, the birth weight is the first nursery weight if taken within forty-eight hours after birth. If an infant is not weighed within forty-eight hours after birth, he is classified in the unknown birth weight category. All infants not previously weighed who die within forty-eight hours after birth are to be weighed and that weight recorded as birth weight.

For statistical purposes any premature infant who remains in the hospital for an indefinite period of time and who reaches 7½ pounds (3,402 grams) will be classified as a survivor. There are two reasons for an infant to remain in the hospital a long time: (1) medical; (2) social. The reason for the somewhat arbitrary selection of the weight level of 7½ pounds is that in most instances at this weight the infant has survived the usual hazards of prematurity. We are obviously leaning over backward in selecting such a high weight level, but we did not wish to miss any infant with the factor of prematurity contributing to death.

2. *Records.*—Two types of records were made up: (1) a worksheet; (2) a statistical report form. The worksheet is the form used to follow all premature infants born or cared for within the hospital. The Statistical Report Form permits study of mortality among premature infants cared for in the hospital in terms of the conventionally accepted birth weight groups and in broad time intervals. Separate forms are to be used for white and nonwhite, and for infants born in or transferred into the hospital.

3. *Establishment of the Procedure.*—The first step necessary is to center the primary responsibility within each hospital on some one staff member for the collection, follow-up, tabulation, and study of the data. It was agreed that in most instances this responsibility should belong to the Pediatric Resident of the hospital, with supervision by the pediatrician-in-charge of the premature center. In a few hos-

pitals which have a well-organized and highly efficient Record Library, the responsibility might belong to the Record Librarian. However, there is a great advantage in making the Pediatric Resident responsible, namely, the stimulation of interest on the part of the House Staff and attending pediatric staff in the general care of premature infants throughout the entire hospital and their introduction to hospital statistics.

At periodic intervals, usually semimonthly or monthly, the responsible hospital staff member will visit all pertinent areas of the hospital—the labor and delivery unit, the premature unit, the "regular" or "full-term" newborn nurseries, the suspect nurseries, the isolation nursery, the general pediatric service, the emergency room, and possibly also the morgue. At this visit, the name of each premature infant admitted to these units since the last tally date will be entered on the worksheet, with the pertinent data on each infant. At subsequent periodic visits, he will check on the course or progress of each infant within the hospital, until the infant has been discharged alive, has died within the hospital, or has reached 7½ pounds. No case will be closed until one of these three terminations has been reached.

4. *Preparation and Submission of Tabulations and Reports.*—Two kinds of tabulations and reports will be prepared: (1) quarterly, and (2) annual. At the end of each quarter of the year, the responsible hospital staff member will prepare a tabulation of all premature infants delivered in, or admitted to, the hospital during a previous quarter. Because of the well-known long period of hospitalization of some premature infants, a three-month lag in tabulation has intentionally been planned. Thus, on July 1 of any year, the tabulation for the quarter January 1 to April 1 of that year will be prepared. The name of the rare infant whose disposition is still not final at the time of the quarterly report will be entered on the report, and the data on that infant will be picked up in the next quarterly report, and the report amended.

The annual report will be tabulated in a similar manner. On April 1 of each year, the tabulations for the twelve months of the preceding calendar year will be prepared.

DISCUSSION

One point of interest brought out by the statistical study in the two hospitals is the discrepancy in the weighing of newborn infants. For example, the weight of an infant recorded in the delivery room immediately after birth might be considerably different from the first weight recorded in the nursery fifteen to thirty minutes later. The difference in the two weighings was as much as 500 to 1,000 grams in individual infants. It was the opinion of the hospital pediatricians that nursery weighings are more carefully done than those in the delivery room. Nevertheless it was agreed to use the first recorded weight of the infant after birth, whether done in the delivery room or in the nursery. Emphasis will need to be placed in hospital surveys and conferences on the need for more accurate weighing when done in the delivery room.

The fact that some of the babies are unweighed at birth or that for others birth weight is unrecorded on birth certificates and hospital records con-

stitutes a great source of error in hospital statistics on premature infants. In this method of securing uniformity in hospital statistics, the names of all babies who are not weighed at birth are entered on the worksheet and are followed to their respective place of care in the hospital; there the weight within forty-eight hours after birth is secured and, if the infant falls within the definition of prematurity, this infant is included in the tabulations.

The New York City Health Department is attacking the problem of infants whose birth weight is unrecorded on birth certificates in another manner also. Each month a list is prepared of the number of all live births in each hospital and of the number of birth certificates in each hospital with birth weight unrecorded. On a monthly basis, a letter is sent to the superintendent and to the directors of obstetrics and pediatrics of each hospital with reported unweighed babies, calling this fact to their attention and requesting that the situation be reviewed in their hospital. Some reduction in the percentage of unweighed babies has occurred by this monthly check. For example, in 1948, 4 per cent of all liveborn babies in New York City did not have their birth weight recorded on their birth certificates; this incidence has been reduced to 0.9 per cent so far in 1950.

One important aspect of securing uniformity in hospital statistics not yet attacked adequately is the need for more careful differentiation between the category of fetal deaths from that of live births. Unfortunately it is not uncommon hospital practice to record as fetal deaths liveborn infants who die in the delivery room in a matter of minutes after birth. There are several reasons usually offered for the practice of recording some early neonatal deaths as fetal deaths: (1) Recording the infant as a fetal death means that the accoucheur needs to fill out only one certificate, as compared with two certificates (the birth and the death certificates) for the neonatal death. (2) Some physicians feel that it is less painful for the parents to accept the fact that they had a stillborn infant rather than a liveborn infant who died shortly after birth. From the broad point of view of pregnancy wastage, the differentiation between stillbirth near term and early neonatal death is an artificial one. In many instances, the cause may be identical. For this reason, the concept of a "perinatal" mortality rate is being considered by some workers. Further clarification of this problem is necessary, and obviously is important in any evaluation of a hospital's premature statistics.

It is obvious that only by accurate statistical analysis of the mortality rates among prematurely born infants within the individual hospital on a periodic basis will the Pediatric Director of the hospital be in a position to know whether improvement is being made in patient care. If significant decreases are observed in the mortality rates after the first twenty-four to forty-eight hours of life, the Pediatric Director can be reasonably confident that the pediatric and nursing care in the nurseries has improved. If there has been no decrease in mortality within the first twenty-four to forty-eight hours of life, the Pediatric Director then knows that the problem may be largely an obstetric one, and that the obstetric staff must be stimulated toward raising the level of ante-

partum and intrapartum care of the mother. Thus, a working tool is placed in the hands of the Pediatric Director within the individual hospital, and he then may approach his obstetric colleagues with the facts.

It is also evident that until such a uniform statistical method is established and in operation in all hospitals in a community, it is impossible to effect any reliable comparison in the mortality rates of prematurely born infants between hospitals. When the method is in effect in all hospitals, it should be possible to evaluate not only the pediatric and nursing care of the premature infant, but also to some extent to evaluate the quality of antepartum and intrapartum care, since a premature birth and a death in a premature infant in a sense may be interpreted as a deficiency in obstetrics in some instances. This latter point of view, namely, the role of the obstetrician, is the more difficult one in which to stimulate community and professional interest.

SUMMARY

This paper describes a study undertaken in New York City to ascertain the completeness and accuracy of previous methods in keeping hospital statistics on the survival rates of prematurely born infants, and describes the current plan established so that each hospital in the community may be assured that its statistics will be complete, accurate, and consistent, and so that some comparability between premature centers may be possible.

DENTAL HEALTH SERVICE AS A FUNCTION OF PREVENTIVE PEDIATRIC CARE

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THE acceptance by the midcentury White House Conference of broad preventive health services as a segment of total pediatric care has created for the participating hospital the additional responsibility for providing community-wide pediatric dental service. It seems reasonable that the children's hospital, offering at present such a wide variety of medical services, should be able with little difficulty to modify existing facilities and personnel so as to coordinate the essential preventive dental measures in a well-rounded clinical teaching program. Ideally, the united efforts of physician, dentist, nurse, and hygienist should seek to incorporate in the usual treatment procedures a broad program of dental health education which shall serve to best advantage the professions and the patient. Mitchell[1] has noted that the trend of present-day pediatric education is to demonstrate to the young physician the benefits he and the community derive from cooperative planning for child health. By active participation in such an integrated program the physician-in-training should develop a better understanding of those everyday problems of dental hygiene which are the reciprocal responsibility of pediatrician and dentist. This firsthand knowledge of the scope of services offered by dentist and dental hygienist encourages professional cooperation, and thereby assures promotion and extension of dental health, a distinct contribution to physical betterment of the growing child.

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THE OUTLINE OF A PROPOSED DENTAL HEALTH PROGRAM

Objectives.—The dental examination in the hospital clinic serves a twofold purpose. In carrying out *prophylaxis,* every effort is made to create a casual atmosphere of patient-dentist cooperation wherein the child may be acquainted with the fundamentals of preventive dental hygiene. In the *corrective* phase of the program, the primary concern is for the patient's well-being. Cheerful acceptance of the patient's questions and suggestions help to allay suspicion and engender in the child a remarkable tolerance for the occasional necessary unpleasant sensations.

Personnel.—The basic dental care unit within the hospital may consist of full-time dental hygienist and dentist, and an actively participating house physician. A dental resident-in-training can be utilized with good result, for experience has shown that only those dentists whose primary interest is working with children will apply for this type of an appointment. A staff dentist, either specially trained

in pedodontics or otherwise suitably qualified, acts in a consultant and supervisory capacity.

Physical Unit and Patient Reception.—When familiarizing the child with the essentials of self-care of the teeth, it is important to stimulate in him a cooperative response. Thus when the patient is first introduced to the dental program an attractive physical unit is essential. To this end the dentist's office and waiting room, separated as much as is practicable from the bustling out-patient department, should be comfortably appointed and colorfully decorated. Perhaps large posters detailing the rewards of proper food selection, conscientious toothbrushing, and regular visits to the dentist brighten the walls. For the older child strategically placed bulletin boards display skillful caricatures illustrating the benefits to personal hygiene and good looks that come from proper dental care. Numerous pamphlets and comic books describing adventures in dental hygiene and nutrition are available in the waiting room for general distribution. The dentist's brightly painted office seems inviting and the reception given each child by the personnel is friendly and unhurried.

Procedure.—Referral to the dental health service is made by the physician in charge of the out-patient department or by a staff member in requesting consultation for a hospitalized patient.

a. *Out-Patient Referral:* During the morning hours the dentist, assisted by the dental hygienist, examines a number of children in need of immediate dental consultation who have not been attended previously by a private dentist and who are referred directly from the out-patient department by the clinic physician. After examining the child, the dentist demonstrates and discusses the important features of the dental examination with the physician. Anomalies of dentition and the tongue, together with acute infections of the oral cavity, constitute the problems of major interest in this typical impromptu clinic, and not infrequently chronic alveolar abscesses with associated localized lymphadenitis will necessitate admission of the patient to the pediatric ward for more complete study and intensive therapy. These admissions, together with occasional patients presenting neoplastic lesions of the mouth and oropharynx, comprise a small but necessarily important group of patients for detailed discussion in the more elaborate conferences participated in by medical students and the hospital teaching staff.

Children with carious teeth, having undergone these complete physical and dental examinations, are given an afternoon appointment for corrective care at a date commensurate with their immediate needs. Although the afternoon program of the dental clinic is largely devoted to such routine corrective measures, here the role of the dentist as an educator is perhaps even more distinguished. At the time of the first visit of the patient (who is then always accompanied by a parent) sufficient time is allowed for the setting of the stage for the dental program proposed for each individual child. The general procedure may be summarized as follows:

(1) Usually the parent accompanies the child into the office, sees him comfortably settled, and then retires to the waiting room.

(2) Instruments are not initially in evidence; when good rapport with the patient has been established they are casually produced and their use is discussed with the child before any procedure is begun.

(3) The hygienist cleans the teeth thoroughly while drawing out the child on his school and home practices of dental hygiene (toothbrushing in vertical strokes, gum massage, carbohydrate excesses in diet, etc.)

(4) The dentist next obtains cooperation of the child and proceeds with a thorough examination of the hard and soft tissues of the oral cavity. After the findings of this examination have been summarized on the patient's dental chart, bite wing x-rays or, if necessary, full mouth films are obtained.

(5) An informal consultation is held by hygienist and dentist with parent and child at which time a plan is offered outlining complete dental needs of the individual. Diet instruction together with a simple perspective of the essentials of dental hygiene are offered together with dietary supplements as necessary; and a kit containing toothbrush and toothpowder is available for gratis distribution.

(6) Before leaving, each patient is given an appointment card by the hygienist who keeps a record of dental services which are contemplated at the time of the return visit. These are divided into prophylactic, restorative and preventive procedures, which latter category includes sodium fluoride applications.

For those children presenting corrective problems referral often can be arranged through the cooperation of the orthodontia department of a recognized dental school whereby consultative and, in special instances, direct patient services may be offered patients as part of the regional dental health program.

b. *Operative Procedure:* Exodontia clinics are held at the hospital for outpatients one morning each week, when a team consisting of anesthetist, hospital dentist and hygienist, and consulting exodontist perform the minor dental surgery required. To the younger age groups the general anesthetic Vinethene is usually administered. Mimeographed form letters detailing preoperative measures (restriction of food intake, time of operation, etc.) are given parents in advance of this appointment. Verbal postoperative instructions are given the child and parent (supplemented by a mimeographed card dealing with saline mouth rinses, cold packs, how to proceed if hemorrhage occurs, etc., and containing date and time of follow-up appointment) before the patient is dismissed. In another group of patients for whom routine surgery (as tonsillo-adenoidectomy or orthopedic operation) is contemplated, the further value of integration of hospital services becomes evident since the necessary dental surgery may often be performed concomitantly. This system reduces patient expenses and usually makes for a shorter period of hospitalization as well. Finally, those groups of children with metabolic dysfunctions, blood dyscrasias, and cardiac or renal disease where surgery is especially hazardous, often must be hospitalized for further evaluation. In such cases requiring extensive oral surgery, or any elaborate routine of premedication, the careful coordination of pediatrician, dentist, nurse, and anesthetist is essential to assure the patient the best possible care.

c. *Hospitalized Patients:* Each child admitted to the hospital is given a toothbrush especially suited to age and dentition. The examining physician notes routinely the dental status of the patient at this time and should request

a dental consultation if there is any evidence of significant oral disease. The duties of the dental team on the ward are twofold. First in importance is the program of dental hygiene education, for experience has demonstrated that the children most frequently admitted to the orthopedic and medical convalescent ward service are those with chronic and debilitating illnesses in whom optimum oral hygiene is certainly a medical essential. A second group readily identified are those repeated offenders admitted again and again in a more or less undernourished, underdeveloped state, suffering from acute illness to which they have been predisposed, at least in some measure, by the poor socioeconomic status of their homes. We feel that it is obligatory that the physician and dentist acquaint these children with the fundamental practices of healthful living, of which dental health is a primary factor. Such children are the source of the most grievous problems in personal hygiene if their needs are not properly anticipated and met under the propitious circumstances afforded by their hospitalization. By diligence on the part of the house staff in requesting dental care for needy patients, and by combining attractive dental health guidance programs (as short cartoons and Technicolor films, friendly toothbrushing competitions with weekly awards, schoolroom quiz contests on dental health facts, and dramatizations by children and dental hygienist of tooth development and protection) in the everyday experiences of the hospitalized child, the important childhood habits of dental care are set in motion.

The second function of the dental team is to make available consultation services to the physician on all patients. Through the years the enhanced value of dental consultations provided under this plan has been apparent in the transformation of the attitude of the medical staff from a concept typified as caries consciousness into an awareness of oral pathology as a reflection of the child's aggregate health. Today the dentist is one of the first specialists to be consulted in cases of rheumatic fever, nephritis, and septicemia, for his facility in frequently detecting important foci of infection has proved invaluable. In studying children with growth disturbances resulting from chronic infection or nutritional or endocrine deficiencies his observations on dentition patterns and oral conditions are essential. Finally, in the restoration of the chronically ill child to total health the dentist's services assume a major significance.

Growing Community Interest.—Perhaps the first official agency to recognize the need for children's dental services was the Dental Division of the United States Public Health Service. In 1948 under the direction of Dr. John W. Knutson this division was instrumental in securing an appropriation of one million dollars to improve dental health services for rural and semi-rural communities. From this fund mobile dental units, fully equipped and staffed with trained personnel, were sent into the field. Such a stimulus has prompted many other official and voluntary agencies to contribute to and encourage perpetuation of community dental health programs.

It is indeed fortunate that today in most areas dental health guidance is a joint endeavor of school, professional, and pharmaceutical groups. Educational programs in the primary grades

rely heavily on the innate respect of the child for the teacher, whose responsibility it is to introduce the mechanical habits of dental hygiene (as toothbrushing and gum massage) together with nutritional guidance in promoting growth foods and school milk and lunch programs. In rural as well as urban communities the interest of school dentists and dental hygienists, either as full or part-time personnel, re-emphasizes for the growing child the importance of routine prophylaxis and early corrective dental care. Pharmaceutical concerns, together with official and voluntary health organizations, make available at negligible cost a wide variety of visual media designed to stimulate the interest of the child in his developing dentition. Through the efforts of these groups pamphlets and charts in a most palatable form have brought into the home for consideration and acceptance dental health facts of concern to the entire family. It is upon the awakening of a community-wide interest in such preventive measures that the success of a children's dental health program depends.

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Case Reports

TRICUSPID ATRESIA WITH A RUDIMENTARY RIGHT VENTRICLE

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THE purpose of this paper is to describe a case of congenital tricuspid atresia with a rudimentary right ventricle without electrocardiographic evidence of left axis deviation or left ventricular preponderance. A brief review of the literature revealed only one similar case previously reported.

CASE REPORT

J. O., a 4-month-old white male infant, was admitted to St. Mary's Hospital, St. Louis, Mo., on Oct. 6, 1950, with a history of severe dyspnea and moderate cyanosis since birth. Some difficulty was incurred in initiating respirations at birth; thereafter, the infant did well in spite of persistent cyanosis. At the time of admission the infant appeared active and robust, having doubled his birth weight of 7 pounds, 6 ounces. He was able to sit up when assisted.

Physical examination revealed an active white male infant with generalized mild cyanosis. A faint systolic murmur could be heard all over the precordium with no associated thrills. The smooth liver edge was felt 1 cm. below the right costal margin and did not pulsate. The radial and femoral pulsations were strong.

Laboratory Work.—Urine was negative, red blood count 5.94 million, hemoglobin 110 per cent, hematocrit 59 vol. per cent, nonprotein nitrogen 40 mg. per cent, blood sugar 67 mg. per cent, and blood Kahn negative.

X-rays.—Examination of the chest in the posterior-anterior view (Fig. 1) revealed decreased bronchovascular markings. The cardiac size was normal. There was a convexity in the region of the right upper cardiac border and another in the region of the right lower border. A concavity along the left upper cardiac border indicated an absent pulmonary conus. The left anterior-oblique view (Fig. 2) revealed a large posterior (left) ventricle and a straight anterior cardiac border indicating an absent or rudimentary right ventricle.

Electrocardiogram (Figs. 3 and 4).—Large peaked P waves were observed in the standard leads, especially in Lead II. There was no evidence of left axis deviation or left ventricular preponderance in either the standard leads or V leads.

Impression.—The cyanosis, polycythemia, and relatively avascular lung fields by x-ray indicated the presence of a cyanotic type of congenital cardiac lesion associated with decreased pulmonary flow. The concavity in the region where the pulmonary conus should appear on the posterior-anterior x-ray view with the straight anterior cardiac border in the left anterior-oblique view was evidence favoring an absent or rudimentary right ventricle with an atretic or hypoplastic pulmonary artery. The upturning of the cardiac apex was thought to be due to the presence of a thick-walled rudimentary right ventricle resting on

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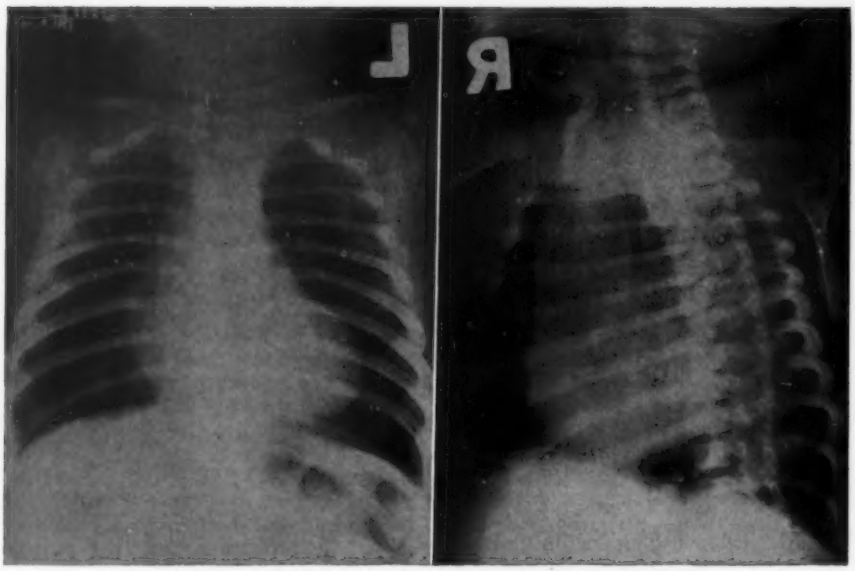

Fig. 1. Fig. 2.

Fig. 1.—Posterior-anterior x-ray view of the chest. Heart normal in size. Lung fields relatively avascular. Double convex right cardiac border. Pulmonary conus is absent and the cardiac apex is upturned.

Fig. 2.—Left anterior-oblique x-ray view of chest. Straight anterior cardiac border. Enlarged posterior ventricle.

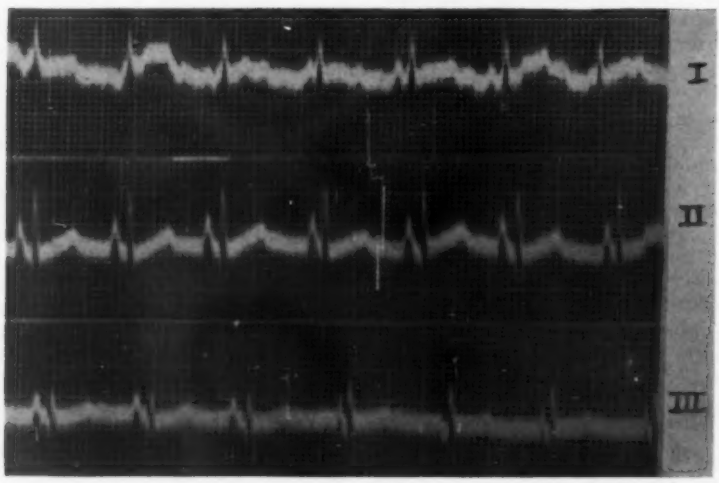

Fig. 3.—Electrocardiogram—standard leads. Note tall peaked P waves, especially in Lead II. There is no evidence of left axis deviation or left ventricular preponderance.

the diaphragm. The convexity of the lower right cardiac border in the posterior-anterior projection with peaking of the P waves in the standard leads of the electrocardiogram favored a dilatation and possibly hypertrophy of the right atrium. The presence of a large posterior ventricle in the left anterior-oblique view indicated left ventricular enlargement.

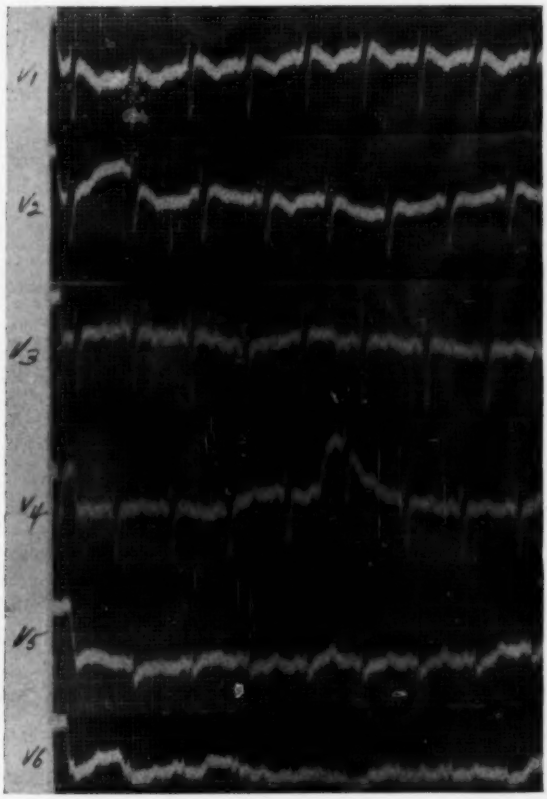

Fig. 4.—Electrocardiogram—chest V leads. Note absence of evidence of left axis deviation or left ventricular preponderance.

In spite of the absence of left axis deviation and left ventricular preponderance in the electrocardiogram, it was felt all other evidence by clinical observation and x-rays favored a diagnosis of tricuspid atresia with a rudimentary right ventricle. Furthermore, it was the clinical impression that, because the liver was small and did not pulsate, a large auricular septal defect existed.

Recommendation.—Surgical intervention to increase pulmonary blood flow.

Operation.—Four days following admission an aortic-pulmonary anastomosis by the Potts-Smith technique was performed through a left mediolateral chest incision. A 4 mm. opening was established between the two vessels. Patency of the opening was confirmed by the presence of a thrill after the anastomosis was completed. The infant tolerated the procedure

well and his color postoperatively was definitely improved.

Postoperative Course.—The immediate postoperative condition of the infant was good. X-rays taken during the twenty-four-hour period following surgery revealed essentially normal lung fields. The infant's condition continued good until thirty-six hours after surgery when severe dyspnea and cyanosis appeared and the systolic murmur previously heard over the operative site was no longer audible. Death ensued in a matter of minutes in spite of vigorous therapy.

Autopsy Findings.—A small amount of sanguinous fluid was found in the left thoracic cavity. The lungs were slightly edematous. The heart appeared slightly larger than normal and, on section, revealed a large posterior left ventricle and merely a rudimentary but thick-walled right ventricle. The tricuspid valve (Fig. 5) was atretic and a large dilated right atrium was found which communicated with the left atrium only by means of a patent foramen ovale. The pulmonary artery (Fig. 6) was hypoplastic and the pulmonary valve opening barely admitted the tip of a probe. The ductus arteriosus was patent. The bronchial arteries were dilated.

The anastomosis at the operative site appeared patent. The immediate cause of death was thought to be due to acute pulmonary edema.

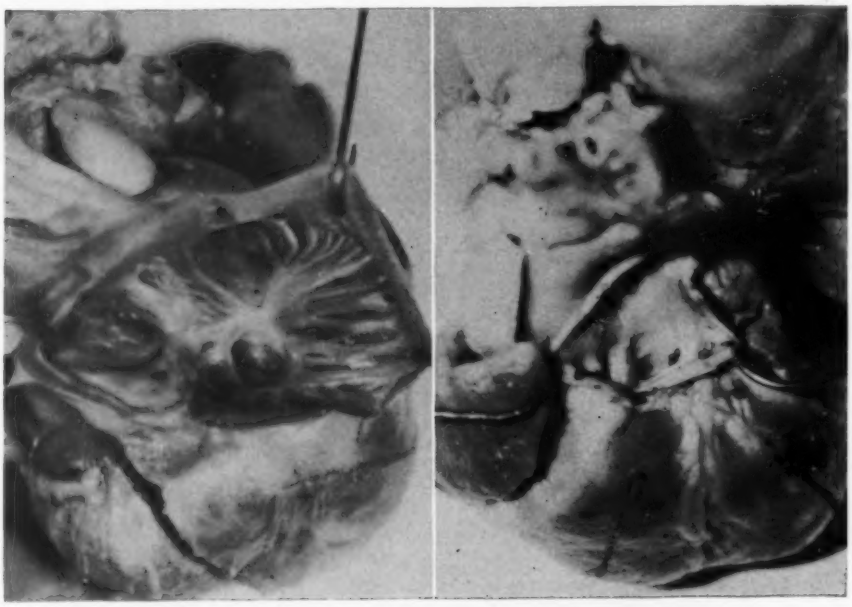

Fig. 5. Fig. 6.

Fig. 5.—Photograph of heart revealing dilated but thin-walled right atrium. The tricuspid valve is atretic.

Fig. 6.—Photograph of heart showing the opened hypoplastic pulmonary artery. Only the tip of a probe could be passed through the pulmonary valve opening into the rudimentary right ventricle.

DISCUSSION

Tricuspid atresia is described as an uncommon congenital cyanotic heart lesion, comprising less than 3 per cent of all cases of congenital heart disease.[1] Most clinicians are agreed that

three features are necessary for the diagnosis, i.e., persistent cyanosis, absence of the right ventricular shadow and of the pulmonary conus on x-ray, and left axis deviation in the electrocardiogram.[2, 3, 4]

Recently, however, Kroop and Grishman[5] demonstrated the absence of evidence of left axis deviation and left ventricular preponderance in the electrocardiogram in a patient with tricuspid atresia with hypoplasia of the right ventricle and without transposition of the great vessels. These authors suggest the possibility that the position and relation of the large right atrium to the diaphragm may affect the rotation of the large left ventricle interfering with the appearance of left axis deviation in the electrocardiogram.

Surgery appears to offer some hope of alleviation of symptoms in this condition. Two procedures have been advocated. First, to increase pulmonary blood flow a Potts-Smith or Blalock-Taussig procedure is indicated. Because most infants with this malformation are quite young at the time of operation, we feel the Potts-Smith procedure is the one of choice. Second, inasmuch as a right to left auricular shunt is necessary for survival, if there is evidence of merely a small auricular septal defect or merely a patent foramen ovale, an operation for creation of a large auricular septal defect is indicated. The technique for this procedure has been described by Blalock and Hanlon.[6] Evidence favoring the necessity for the second procedure is a very large or pulsating liver and/or a large right auricle demonstrated by x-ray. Absence of these criteria, however, does not necessarily indicate the presence of a large auricular septal defect, especially in the very young infant. It was felt the small size of the nonpulsating liver and the minimal right auricular enlargement demonstrated by x-ray in the case described indicated to us the presence of a large auricular septal defect. Angiocardiography possibly would have proved this erroneous.

The operative procedure performed on this patient definitely improved his color postoperatively. The cause for the sudden death of this infant thirty-six hours after surgery could not be determined. Most probably death was due to pulmonary congestion. Perhaps, if an auricular septal defect had been created, pulmonary congestion would not have occurred.

SUMMARY

1. A case of tricuspid atresia with a rudimentary right ventricle without electrocardiographic evidence of left axis deviation or left ventricular preponderance is described. A brief review of the literature revealed only one similar case previously reported.

2. The electrocardiographic changes and indications for surgery in this condition are briefly reviewed.

Note: Since this paper was accepted for publication, H. L. Abrams and R. H. Alway in *Pediatrics* **7**: No. 5, May, 1951, reported an additional case of tricuspid atresia without left axis deviation.

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REDUPLICATION OF THE STOMACH

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REPRODUCTIONS of the gastrointestinal tract are a relatively uncommon occurrence. The term "enterogenous cyst" has been applied to these reduplications, which may occur in any part of the gastrointestinal tract from the esophagus to the sigmoid. They are most commonly seen in the ileocecal region and decrease in frequency generally proximal to this point. About fifteen cases have been reported in the literature as occurring in the duodenum, and the case reported herewith is the fourth recorded instance of reduplication of the stomach. The third recorded case was reported by one of us (G.T.M.) in 1948. Illustrations of this case are included in this paper.

Enterogenous cysts are closely related embryologically to congenital diverticula. Meckel's diverticulum occurring as a failure of closure of the omphalomesenteric duct is the commonest form of congenital diverticulum. Cysts occurring in this region represent remnants of this embryological structure. These cysts, wherever they occur in the intestinal wall, may be intermuscular, submucosal, or subserosal, or may occur as a reduplication anatomically similar to the normal gastrointestinal tract which they duplicate, as in the case of reduplication of the stomach reported by Ladd and Gross. In isolated instances, cysts have lost their connection with the wall of the intestine and may occupy a position between layers of the mesentery somewhat removed from the parent gut. The uniform characteristics of these cysts is that the structure of the cyst wall resembles the intestinal wall from which it was derived. Occasionally, intracystic pressure or inflammatory changes may produce variations in the epithelial lining of these cysts.

The symptoms produced by these cysts in the intestinal tract vary with their location and are usually manifested by evidence of obstruction, infection, or both, and rarely by the presence of a palpable mass. Most often symptoms are produced which lead to recognition of these cysts at laparotomy in early infancy, but our first patient with reduplication of the stomach was 27 years of age. The preoperative diagnosis of such a cyst is extremely unlikely, although a presumptive diagnosis may be made rarely in the presence of a palpable mass with obstructive symptoms.

Treatment of enterogenous cysts has varied widely with different observers and it may be said that each cyst presents a problem which must be solved individually. Removal of a cyst without entering the bowel lumen is frequently impossible because it is so intimately attached to the wall of the bowel. Resection of the bowel and its contained cyst is usually the method of choice. In cysts of the duodenum, resection or total removal may be impossible because of the danger of damage to the common or pancreatic ducts. Attempts to drain these cysts externally have usually resulted in failure because of their tendency to recur. External drainage of such cysts was attempted in two of the patients with enterogenous cysts of the stomach previously reported and apparently was successful in the case of Ladd and Gross. The method of internal drainage suggested by Gardner may be the method of choice in some instances.

The case reported by Ladd and Gross was that of a 7-year-old girl whose reduplication of the stomach

closely simulated the adjacent normal stomach. The symptoms which led to a laparotomy were a vague gastrointestinal disturbance and roentgen-ray evidence of encroachment on the normal stomach lumen along the greater curvature. Treatment consisted of marsupialization of the mass with subsequent débridement and packing with gauze. The case of Ferraro occurred in a 6-month-old child. Symptoms consisted of the presence of a mass in the upper quadrant which was incised when the child was 6 weeks old. The operative area continued to drain a watery fluid until laparotomy was performed at the age of 6 months. At operation the cyst was removed from the stomach along with a small portion of the stomach wall. The

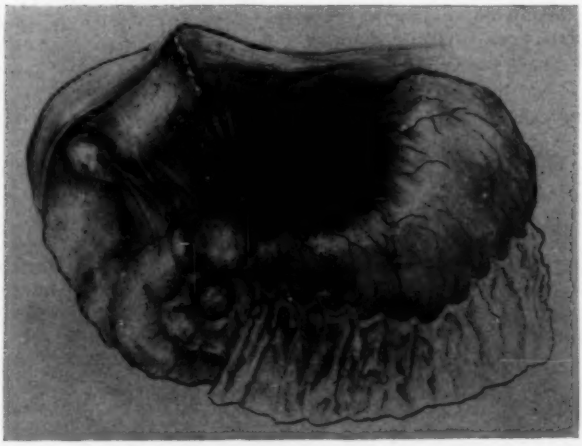

Fig. 1.—Reconstructed drawing of cyst in situ at distal end of stomach. The major portion of the cyst was imbedded within the wall of the stomach.

Fig. 2.—Cyst after removal. Larger portion of hourglass-shaped mass was that imbedded in stomach.

wound healed well, and recovery from the cyst was apparently satisfactory. The child died later of worm infestation and malaria. The patient whose case we reported in 1948 was 27 years of age. X-ray films showed evidence of pressure on the lower end of the stomach. Intermittent pain and fever were the other presenting symptoms. The cyst was easily removed at laparotomy.

CASE REPORT

H. H. H. (No. 50489-Columbia Hospital).—This 5-month-old female infant was first seen in consultation with Dr. Thomas Talbert on June 27, 1950. Her difficulties began during the second week of life with frequent vomiting and mild diarrhea. The vomiting was sufficiently severe to necessitate hospitalization for parenteral fluids. The vomiting was not projectile, and the stools were described as being dark greenish black, soft yellow, and on one occasion containing particles of old blood. She was hospitalized for ten days at 2 weeks of age, and during that time did little or no vomiting and the diarrhea gradually improved. However, during this period she lost 6 ounces in weight. Gastrointestinal series was reported to be negative.

During the ensuing five months the infant had a rather rocky course with periods of vomiting interspersed with bouts of diarrhea. The stools at times contained bright red blood and at other times appeared black. The stools between the bouts of diarrhea varied from normal yellow to grayish putty color. In number the stools varied from three to ten per day. The patient took various formulas fairly well but refused solid foods, cried excessively, and passed large amounts of gas by rectum. The patient did not gain weight properly. During the first five months of life she gained only 3½ pounds.

At no time did the patient have fever and, other than restlessness, did not appear ill.

Past History.—Full-term, normal spontaneous delivery. Birth weight, 8 pounds, 3 ounces. Vitamins were given for only one week, beginning at the age of one month.

Family History.—Essentially negative except that one sibling had a meningomyelocele and the paternal uncle and aunt had hay fever.

Physical Examination.—Temperature was 99° F. (rectal); weight 11 pounds, 10 ounces; head 15 inches; length 23 inches. Other than the patient appearing quite pale and somewhat small for her age, nothing abnormal was found. The abdomen was prominent and moderately distended but there was no tenderness or palpable masses.

Laboratory Findings.—Laboratory findings showed hemoglobin 42 per cent; red blood count 2.6 million; white blood count 11,200; differential—polymorphonuclears 45 per cent, lymphocytes 50 per cent, mononucleosis 2 per cent, eosinophiles 3 per cent. Urinalysis was negative. Stool culture was at first reported positive for *B. dysenteriae.* However, the culture was sent off for further study and was reported three weeks later as negative for pathogens. Trypsin test on stools (x-ray film test) was positive on three occasions. Benzidine test on one stool specimen was negative. Glucose tolerance test (micromethod) was normal.

Course in Hospital.—The patient was given two blood transfusions of 115 c.c. each. The hemoglobin rose to 80 per cent and the red blood count to 4.1 million. Following this, patient was put on iron by mouth (2 c.c. t.i.d.). On this admission, the patient remained in the hospital nine days. There was little or no vomiting, and the stools were loose and brownish in color (averaged three to five per day). At no time was any bright red blood reported in the stools. The patient took goat's milk and Nutramigen formulas reluctantly and refused all solid foods. The patient did not gain weight. Because the stool culture was reported positive for *B. dysenteriae,* the patient was put on sulfadiazine and sent home to continue on this,

iron and lactic acid formula, and vitamins.

The patient was not seen again for eighteen days when she was checked and found to have a hemoglobin of 30 per cent and had not gained weight. Stools were reported to have been black and also on several occasions contained bright red blood. At this time the report on the stool culture sent off for further study was returned negative for pathogens. The examination at this time was again essentially negative. After repeated transfusions the hemoglobin and red blood count rose to normal figures. An exploratory laparotomy was done on Aug. 2, 1950.

Operation.—An upper midline incision was made to expose the peritoneal cavity. An indurated mass was found in the mid-portion of the abdomen. Dissection was carried out in this mass, and a Meckel's diverticulum

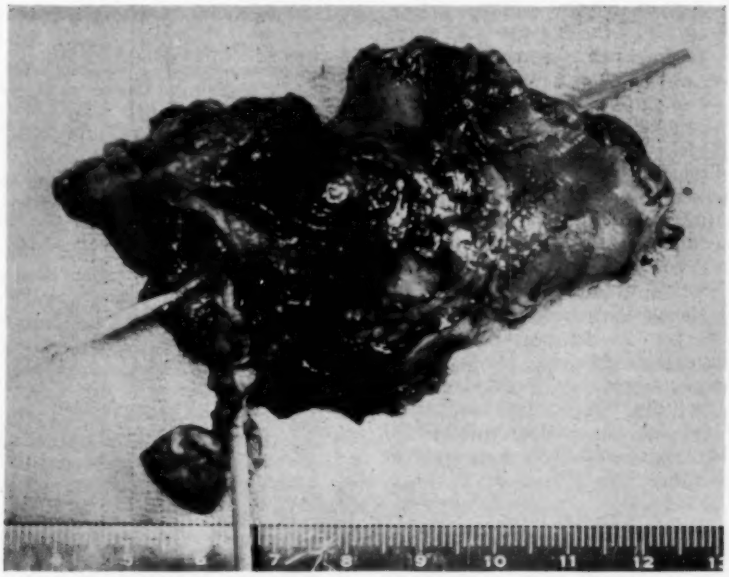

Fig. 3.—Photograph of specimen removed from patient here reported. Stick passing diagonally is through cavity of duplicated stomach. Stick passing perpendicularly is through lumen of Meckel's diverticulum which communicated with duplicated stomach and ileum.

patient was re-admitted to the hospital for further study and repeated blood transfusions. A gastrointestinal series revealed a normal upper gastrointestinal tract. On two occasions it was impossible to pass barium beyond the mid-portion of the transverse colon. There was no apparent reason why the colon refused to fill.

A surgical consultation was requested because the patient was obviously losing blood from somewhere in the gastrointestinal tract. Physical

communicating with the ileum was found. The tip of the Meckel's diverticulum communicated with a cavity attached to the lower border of the stomach. Investigation of this region revealed that there was a reduplication of the stomach. The second stomach was about the size of the normal stomach and attached to the greater curvature. This reduplicated stomach was removed from the greater curvature of the normal stomach, without entering the cavity of the

stomach. The raw surface of the greater curvature was sutured with interrupted sutures 00 chromicized catgut and reinforced with interrupted sutures of No. 40 cotton. Meckel's diverticulum was ligated near its base, amputated, and stump inverted. Drain was placed down to the area of the mass, and brought out through the stab wound in the left flank. Wound was closed in layers, with interrupted No. 40 cotton for the skin.

Pathological Report.—The pathological report showed a structure closely resembling a normal stomach in gross appearance. Microscopic examination showed the usual components of the stomach wall. The structure which communicated with the ileum and duplicated the stomach had the gross appearance of a Meckel's diverticulum but was not subjected to microscopic examination.

Course Since Operation.—After the reduplication of the stomach was removed, the patient did extremely well. She was put on an evaporated milk formula and solid foods. Her appetite became excellent and she gained weight rapidly. When last seen at 10 months of age, the patient weighed 20 pounds, a gain of almost 9 pounds in four months.

SUMMARY

1. The fourth recorded case of duplication of the stomach is reported.

2. The unique feature of this case was a communication with the ileum through a Meckel's diverticulum.

3. Intestinal bleeding was the most prominent symptom.

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DIPLOCOCCUS CRASSUS MENINGITIS

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CLINICAL infection due to *Diplococcus crassus* was not described in American literature until 1951. Septicemia in a premature infant was reported by Cardullo, Schulman, and Smith[1] along with a review of 152 cases from European sources. Only eleven of this series occurred in children.

CASE REPORT

S. A. was a 6-year-old white female admitted on Feb. 4, 1949, because of high temperature and headache. The past and family history were noncontributory. Onset was abrupt, on February 1, with fever, headache, and the vomiting of greenish yellow mucus that was tinged with blood. There was also anorexia and a complaint of back pain, but not of stiff neck. She had a generalized convulsive seizure on the second day of illness and became disoriented. Her expression was one of staring. Treatment was begun on the first day of illness with oral penicillin. She did not improve and the day before admission developed "spots and blotches" and a stiff neck. Hospitalization was advised by her physician.

When first seen, the child was lying on her side in marked opisthotonos. She was well developed, but thin and moderately dehydrated. Her temperature was 103.4° F. rectally, pulse 120, and respirations 24. Photophobia and hyperirritability were also present. There were petechiae and purpuric areas of the legs and forearms. The tonsils were hypertrophied and the pharynx and tonsils were inflamed. The neck was rigid and hyperextended. The chest was clear and the heart sounds were normal; the abdomen was negative. Both the Kernig and Brudzinski signs were positive. Deep reflexes could not be elicited and cutaneous hyperesthesia was present.

Erythrocyte count was 4.86 million with 85 per cent hemoglobin. Leucocyte count was 12,000 with 84 per cent neutrophiles and 16 per cent lymphocytes. Spinal fluid cell count was 314 with 218 white blood cells; 66 per cent neutrophiles and 34 per cent lymphocytes. Spinal fluid sugar was 44 mg. per cent, chlorides 750 mg. per cent, and protein 49 mg. per cent. Culture of the spinal fluid grew a diplococcus that was predominately positive to the Gram stain, but negative organisms were also seen. Fermentation studies were positive for lactose as well as glucose, maltose, levulose, and sucrose; thus identifying it as *D. crassus*. Blood cultures, Kahn, urinalyses, and chest x-ray were negative.

Therapy consisted of intravenous fluids (⅙ sodium r-lactate, saline, and 5 per cent glucose in distilled water), penicillin 100,000 units every three hours, and sodium sulfadiazine 1.33 Gm. (27 c.c. of 5 per cent solution) every eight hours. By the following morning, the patient was taking oral fluids satisfactorily and was better oriented; temperature was 100.6° F. rectally. Parental sulfa was discontinued and sulfadiazine 1 Gm. every four hours was begun by mouth. Treatment was continued for ten days; sulfadiazine blood level varied from 18 to 8 mg. per 100 c.c. Rapid recovery ensued, skin lesions faded in a few days, and the spinal fluid on the fifth hospital day was normal. Patient was discharged recovered on the fourteenth hospital day.

COMMENTS

This patient was believed to have meningococcic meningitis with meningococcemia until *D. crassus* was iso-

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lated in pure culture from spinal fluid. Jaeger[2, 3] described *D. crassus* in 1895 as a meningococcus and identified it as a species in 1903 by its growth on gelatin at room temperature, fermentation of lactose, and its resistance to drying. Standard textbooks on bacteriology described *D. crassus* as normal flora of the nasopharnyx that is usually found only as a contaminating organism with other infections of the central nervous system, middle ear, and mastoid following trauma, such as skull fractures.

According to Chevalier, Lévy-Bruhl, and Bernard,[4] mice, guinea pigs, and rabbits were not infected by intravenous, intraperitoneal, or intracerebral injection of *D. crassus*. However, Bordes, Ceccaldi, Palinacci, and Berthon[5] duplicated a case of fatal meningitis in a monkey with the organism isolated from their patient. It is not unusual for species virulence to vary. *D. crassus* has been reported to be agglutinated by antimeningococcal serum at times.[6, 7, 8] The organism isolated by Cardullo and associates[1] was sensitive to 10 mg. per cubic centimeter of sulfadiazine, 36 mg. per cubic centimeter of aureomycin, and 10 u. per cubic centimeter of penicillin. S. A.'s recovery was prompt and uneventful on standard antimeningococcal treatment.

Although this is not likely to become a very important etiological agent of disease, it is possible that it may be recognized more frequently if proper interpretation of staining and fermentation tests are done.

SUMMARY

A case of meningitis due to *D. crassus* is reported. Prompt recovery followed penicillin and sulfadiazine therapy.

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Medical Progress

ROENTGEN THERAPY IN LYMPHADENOSIS* AND SINUSITIS IN CHILDHOOD

With Ten-Year Follow-up of 349 Cases

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ROENTGEN therapy is a valuable adjunct in the treatment of certain conditions of the ear, nose, throat, and chest in childhood due to the fact that it has a beneficial effect on infected and hyperplastic lymphatic tissues simultaneously. Despite the fact that the problem of infection has been greatly reduced by the chemotherapeutic and antibiotic agents and that surgery remains the best method for complete removal of most of the hyperplastic lymphoid tissues (especially the tonsil and adenoid), there remains a group of conditions in which x-ray therapy is, or should be, the treatment of choice.

Since 1937 I have treated and observed over 1,400 patients, of whom about 200 were from the Radiation Therapy Clinic† of Beth-El Hospital, Brooklyn, N. Y. The patients were obtained through the courtesy of the Pediatric and E. N. T. Clinics.

It is the purpose of this paper to present some of the diagnostic and therapeutic data acquired during the course of this work, as well as a summary of 349 patients treated during the preceding ten years and followed up in January to March, 1951.

HISTORY

The use of x-ray therapy in benign conditions of the nose and throat is not a recent innovation. In 1905 Heineke[1] in Leipzig was the first to prove the selective destructive effect of x-rays upon lymphoid tissue. The first American report was by Osmond[2] of Cleveland in 1916, who made the observation that after a few roentgenograms many of his sinus patients seemed to be improved. He treated several and reported twelve cases with excellent results in 1923. In 1919 Witherbee[3, 4] treated sixty patients with hypertrophied tonsils and felt that a valuable therapeutic aid was available in x-ray therapy. Numerous papers have appeared in the literature since that time reporting thousands of patients treated by this method. Among the more extensive reports are those by Williams and Bryan,[5] Warren,[6] Hubeny and McNattin,[7] Butler and Woolley,[8, 9] Hodges,[10] Desjardins,[11] and others. Rathbone[12, 13] of Washington made a special study of these conditions in childhood starting in 1932 and

*Dr. Bela Schick and I coined this term to describe the condition characterized by chronically infected hyperplastic lymphoid tissue of the Eustachian tube, nasopharynx, pharynx (also called granular pharyngitis), adenoid, tonsil, and cervical, retropharyngeal, and perihilar glands. The frequency with which all or most of these structures is so involved seems to require recognition as a syndrome.

†Dr. H. I. Teperson, Chief.

the results of treatment in the first seventy patients were published in 1937. By 1939 he had treated over 500 children.* Laing[14] reported favorable results in 900 children with sinusitis in 1948.

One of the most important advances in this field, the use of radiation for the prevention of deafness, was made by Crowe and his associates in a series of investigations starting in 1937[15, 16, 17, 18, 19] and since used widely with good results by many observers.[20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31]

Treatment of the tonsil and adenoid by radiation has had many advocates like Gibert,[32] Birk,[33] Zoepffel,[34] Torres-Carreras,[35] Schulte,[36] and others in the early literature. Recently there have appeared a number of rather favorable reports from widespread centers differing only from the earlier ones in the larger numbers of cases reported and the length of time the patients were observed. The most noteworthy were the papers of Rossitto,[37] Fricke and Brown,[38] and Uhlmann and associates.[39]

It is fairly evident that radiotherapy in these conditions is neither new nor in a very early stage of development. Pohle[40] states that in certain types of cases, "no other form of therapy has so much to offer. . . . Furthermore the experimental stage is past and we now know much more accurately the uses and limitations of the method."

ANATOMICAL AND DIAGNOSTIC CONSIDERATIONS

A. *Lymphatic Hyperplasia* (Lymphadenosis).—The major difference between nose and throat conditions in children and adults lies in the fact that children have a relative abundance of lymphoid tissue in these regions.[41] The lymphoid tissue swells during the acute infection and may thus cause obstruction.[42] For example, such tissue in or near the Eustachian tube may lead to otitis media. If the lymphatic tissue obstructs the ostia of the sinuses, the resulting poor aeration to that region predisposes to antral or ethmoidal infection. Occasionally cervical glands draining the tonsillar area become acutely involved. Subacute or chronic tracheobronchitis may be associated with enlargement of the peritracheal or peribronchial lymph glands. It is for this reason that upper respiratory infections in children are so often complicated by otitis media, acute sinusitis, cervical adenitis, and bronchitis. Therefore, it must be remembered that these conditions are closely interrelated and more or less dependent on each other. This is demonstrated graphically in Fig. 1.

B. *Sinusitis.*—Infection of the nasal accessory sinuses occurs far more frequently in children than one would ordinarily suspect. Davis[43] and Scammon[44] found the maxillary sinus present as an oval pocket at birth and pneumatization of the lateral ethmoidal mass usually complete at birth. The sphenoid is very small in the first year and the frontal is barely visible before the third year. Yet infection of the maxillary antrum is very frequent in young children. Nippe[45] has stated that sinusitis "now ranks as one of the common diseases in childhood." Campbell[46] has written that no infant reaches the age of one year without a sinus infection. Leroux[47] has said that "ethmoid disease is very common in children even after the adenoids have been removed and these children have repeated colds and stuffed noses." Can-

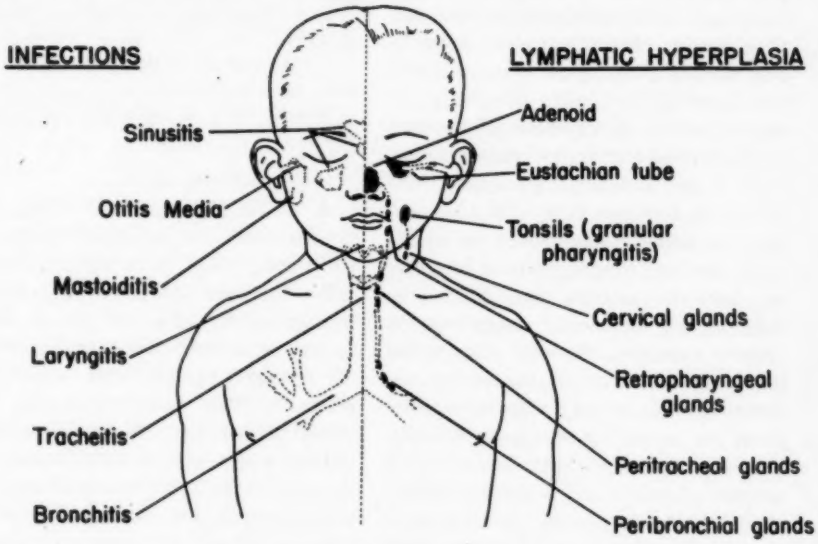
*Personal communication.

ANATOMY AND PHYSIOLOGY

RESPIRATORY TRACT INFECTIONS OF CHILDHOOD DIFFER FROM THOSE OF ADULTS BECAUSE OF THE FREQUENT PRESENCE OF INFECTED HYPERPLASTIC LYMPHATIC TISSUE, WHICH COMPLICATES THESE INFECTIONS IN TWO WAYS:

1. By acting as an additional focus of infection
2. By interfering with proper drainage.

GRAPHICALLY, THE TWO CONDITIONS ARE INTERRELATED AS FOLLOWS:



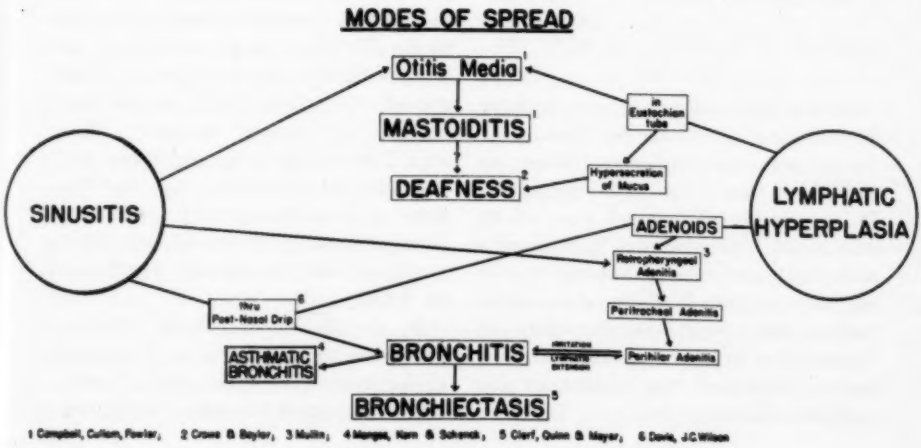


Fig. 1.

tor[48] found sixty-seven of 100 children to have sinus infection at the E. N. T. Clinic, Children's Hospital, Melbourne, Australia. Schoenberg[49] found that 154 (66 per cent) of 232 nurslings showed empyema of one or more nasal accessory sinus on autopsy. Cullom,[50, 51] Fowler,[52] and many other otolaryngologists and radiologists have demonstrated sinus disease in nearly every case of infantile and childhood otitis media. By this route, sinusitis may also be a frequent primary focus for mastoiditis.[52, 53, 54] Similarly, it may act as the point of origin in cases of bronchitis,[12, 55, 56, 57, 58] bronchiectasis,[59, 60] and asthmatic bronchitis.[12, 61, 62] In a fourteen-year study on recurring and chronic cough in childhood, Brown[63] found chronic bronchitis, bacterial asthma, and bronchiectasis almost invariably dependent on chronic sinusitis. Stoloff[64] stresses the importance, "in all instances of suspected asthma or any respiratory distress, to examine roentgenologically not only the chest but the neck and sinuses as well." It seems necessary, therefore, to emphasize the fact that sinusitis is much more frequent than is commonly recognized.

GENERAL INDICATIONS FOR RADIATION THERAPY

On the basis of my experience there are certain indications for the use of radiation therapy either exclusively or in conjunction with other treatment. It should be emphasized that every case must be considered individually and that very often, perhaps in the majority of cases, there are several factors which may make the choice of treatment a perplexing problem. In general, however, the indications for radiation therapy are:

1. Lymphadenosis

(a) In the young child (under 5 years of age).

(b) In children of all age groups with Eustachian tube obstruction (as evidenced by diminution of hearing), or granular pharyngitis, chronic or recurrent cervical adenitis, etc.

2. Sinusitis (subacute or chronic) where the usual therapeutic aids (penicillin, etc.) have failed, but before surgery is contemplated.

3. Lymphadenosis with or without sinusitis

(a) In the chronically ill child (cardiac, tubercular, etc.).

(b) In the "nonallergic" asthmatic child.

1. *Lymphadenosis.*—

A. *In the Young Child:* The ideal type of case for roentgen therapy is the young child with diffuse chronically infected lymphoid hyperplasia throughout the nose and throat with a watery or mucous discharge, a history of frequent colds, and a chronic cough.[12] Most otolaryngologists and pediatricians hesitate to recommend tonsillectomy and adenoidectomy on infants under 4 or 5 years of age. On the other hand, such patients are frequently helped by roentgen therapy, and the benefit is usually a permanent one. After roentgen therapy the children will have fewer colds, and the sinuses rarely become involved. If involved, they clear up in a few days without any special therapy. Many such infants can be carried along until they are old enough to have tonsillectomy and adenoidectomy performed. The problem of tonsillectomy versus radiation will be further commented on below.

B. *In the Older Child:* Another group are children who have frequent colds, and with every cold develop either an attack of otitis media, mas-

toiditis,[65] or cervical adenopathy. These invariably have a diffuse lymphoid hyperplasia throughout the nose and throat with large adenoids. Adenotonsillectomy may stop the attacks of cervical adenopathy but it frequently has no effect on the child with repeated otitis, or increasing deafness. This is due to the horizontal position of the Eustachian tubes and to the lymphoid hyperplasia around or within the orifices of the tubes, so that surgical removal is often impossible. It has long been an established fact that this lymphoid tissue yields readily to small doses of roentgen therapy. Crowe[15, 16, 17, 18] has stated that if "the causal condition is recognized and properly treated with radiation as early as possible to insure normal functioning of tubes, the number of deaf adults in the next generation could be reduced by 50 per cent."

Radiation therapy is also effective in cases of granular pharyngitis (regrowth of tonsillar and adenoid tissue after tonsillectomy), chronic or recurrent cervical adenitis,[66] retropharyngeal abscess,[67] and chronic nonspecific hilar adenitis.[5, 68]

2. *Sinusitis.*—In 1938, commenting editorially on the work of Hodges[10] and others in sinusitis, Kaplan[69] claimed that "irradiation is rapidly being accepted as the therapy of choice in treatment of inflammatory conditions throughout the body." The advent of the sulfonamides and antibiotics, of course, has changed this, but radiation still can be used to advantage. I have had little or no occasion to treat acute sinusitis, as suggested by Popp and Williams[70] and others, especially since the advent of penicillin, which has been most effective either in aerosol or by intramuscular route.

However, the child who does not respond should have the opportunity to be treated by radiation before surgery is contemplated.

3. *Lymphadenosis With or Without Sinusitis.*—A. *In the Chronically Ill Child:* As Pohle[40] and Knox[71] have pointed out there is a group of children suffering from cardiac or other debilitating chronic diseases complicated by chronic sinusitis or lymphadenosis. Here one would undoubtedly hesitate to advise tonsillectomy or any other surgical procedure. There can be little argument that this is the type of case par excellence for radiation therapy.

B. *In the Asthmatic Child:* The treatment of asthma in children often presents a difficult problem. Whether or not all asthmatic cases are due to allergy alone is a most questionable point. It is certain, however, that many of the so-called cases of asthmatic bronchitis in nonallergic children are complicated if not initiated by chronic sinus disease,[26, 27, 72, 73] lymphadenosis, and occasionally hypertrophied hilar lymph glands. Lierle[61] studied twenty patients with asthma and found all to have varying degrees of sinusitis. Manges[37] reported 354 cases of asthma with sinus involvement in 60 per cent. I have had several experiences in asthmatic children like those reported by Crowe and Ward[74] in which the usual "antiallergic" treatment failed but where irradiation of the nasopharynx decreased the frequency and severity of the attacks. These children most often had frequent colds, and with each cold usually developed asthma, often severe. Continuing this work Ward and associates[75] studied thirty-four children and reported excellent results in 68 per

cent. It should be noted that about half of these children had undergone tonsillectomy and every one of these showed regrowth of the lymphoid tissue in the nasopharynx. After irradiation twenty-three of the thirty-four children showed the nasopharynx to be completely free of such tissue:

The high incidence of sinusitis in patients with bronchiectasis (82 per cent reported by Clerf[59]) perhaps accounts for some of the good results reported for radiation therapy in the latter.[76, 77]

My experience in vasomotor rhinitis and other allergies does not coincide with that of Warren[6] and radiation is not used except where the allergy is complicated by sinusitis or lymphadenosis.

RADIATION THERAPY VERSUS TONSILLECTOMY

There has been a great deal of criticism of the tendency toward indiscriminate and excessive tonsillectomy and adenoidectomy since as early as 1901 by Bosworth[78] and through the years to Fabricant,[79] Kaiser,[80, 81, 82, 83, 84, 85] and Bakwin.[86] The studies of Shea,[87] Selkirk and Mitchell,[88] and Kaiser[89] showed greater incidence of sinusitis in tonsillectomized than in nontonsillectomized children. Bullen[90] reported that allergy was more frequent in tonsillectomized than in nontonsillectomized children. Peshkin[91] found that asthma was aggravated more often than aided by tonsillectomy.

The whole problem was excellently reviewed by Denzer and Felshin[92] who pointed out that the apparently simple decision whether or not to remove the tonsils and adenoids is actually extremely complex. Of 217 cases referred to them, only thirty-seven or 17 per cent required tonsillectomy after careful study and investigation. They concluded that "there is a tendency for the operation to be performed as a routine prophylactic ritual for no particular reason and with no particular result."

However, in many of these reports insufficient attention has been paid to the importance of the age factor which has been emphasized by the studies of Sydenstricker,[93] Wilson and collaborators,[94] and many others. Ward and associates[75] found lymphoid hyperplasia after tonsillectomy in all of the children in their study on asthma. The average age was 4 years. If Selkirk and Mitchell's[88] detailed chart of 130 cases is divided into those operated on before and those after six years of age, it is found that eighteen had slight and ten marked hypertrophy of lymphoid tissue in the young group, while thirteen had slight and only four marked hypertrophy in the older group. In other words, the older the child at operation the better the results of tonsillectomy. This has been my clinical experience.

More and more emphasis is being placed on childhood emotional experiences. Coleman[95] and others have emphatically pointed out the psychological advantage of performing tonsillectomy at as late an age as possible since the need of the younger child for "sustained security may be even greater than in the older who is able to adjust more easily. . . . Furthermore under three and a half years a child is as yet unable to verbalize his fears. . . . The impact of tonsillectomy may be the trigger mechanism that is disastrous in an already sensitized personality." Obviously, the older

the child when tonsillectomy is performed the better the preparation and the more opportunity to maintain the emotional integrity of the child.

Roentgen therapy will never replace tonsillectomy since the actual volume of lymphatic shrinkage that can be obtained by radiation is much less than that obtained by surgical removal. However, radiation presents certain advantages. First, one is able to reach areas that could not be reached by surgery; second, it may be used during epidemics of poliomyelitis; third, it may be used in the presence of active infection. Therefore, if one would prefer to postpone tonsillectomy in a child for one or several of the above reasons and yet effect some lymphatic shrinkage, roentgen therapy is the treatment of choice.

TECHNIQUE

Various techniques have been advocated with doses and intervals varying from 20 r daily for a week[5] to 500 r in one single dose.[96] Since larger doses have not appreciably improved the percentage of successful results, I have used relatively small doses, 50 r at 135 KV with ¼ mm. copper and 1 mm. aluminum filtration on each of two lateral portals in the cases of lymphadenosis. The child lies prone with the head first toward one side then the other. The area is screened off by lead shields with the opening about four inches long and two inches wide bounded by the upper edge of the ear, the descending ramus of the mandible and back toward the mastoid area. The angle of entry is slightly upward and forward so that the rays pass through the tonsillar and nasopharyngeal area. If the sinuses are involved an additional 50 r are given through an anterior portal screening the eye and eyebrow. If there is peribronchial hilar adenitis a dose of 50 r is given to the anterior chest.

Such treatment is administered once a week for five to ten weeks depending on the severity of the involvement and the clinical improvement. The latter has been generally unpredictable, however, since some patients show much greater shrinkage of lymphatic structures than others.

RADIUM VERSUS X-RAY THERAPY

While there are many champions for the use of radium, I, like Youngs and Woutat,[97] Uhlmann,[39] Tyler,[98] and many others, feel that radiation therapy is preferable, especially in small children, for several reasons. First, it is easier to administer since by utilizing this technique one need not hurt the child with nasal applicators. Second, the need for anesthesia, local analgesia, or other manipulation is obviated. Third, radiation gives more widespread effect and in the younger child there is likely to be lymphatic hyperplasia throughout the nasopharynx as well as the Eustachian tube, while radium is effective only within a few millimeters of its focus of application. Fourth, dosage can be more accurately calculated to reduce one of the hazards.

DANGERS

No untoward effects of any kind were noted in this series of patients. This coincides with the experience of other workers in this field. Rathbone[12] flatly states "because of the very small dose, the treatment is absolutely harmless, and without any immediate or late ill effect." Crowe and Walzi[18] find that "these relatively small doses

which in no way injure the pituitary gland, nasal pharyngeal mucosa, or inner ear make danger negligible." Uhlmann[39] in continued observation of 480 patients over a ten-year period states it to be "without danger under proper execution." From Epifanio and Cola's[99] study, Warren[6] concluded that 5 to 10 per cent of the dose reaches the hypophysis. Nerve tissue generally is highly resistant to deep x-ray therapy. Alpers and Pancoast[100] found no changes of consequence in the brains of patients who had received x-ray therapy for brain tumors (and therefore much larger doses). Kaplan[101] reported that the normal thyroid gland is highly resistant to radiation. Patients treated for malignancies of the neck and larynx receive heavy irradiation of the thyroid yet rarely if ever is myxedema produced. Zoepffel[34] reported no ill effects in fifty children after radiation for tonsillar hypertrophy. Tonsillectomy subsequently performed on some of the patients was not associated with more profuse hemorrhage or other incident attributable to the roentgen treatment. My experience has been similar. Several of the irradiated tonsils examined by a pathologist* were found to show little or no changes except for some diminution in the lymphoid elements, Butler and Woolley[8, 9] in experiments on cats found "no damages to normal structures and if treatment fails, no interference with subsequent surgery."

A word of caution is sounded by Robbins and Schulz[102] who report some ill effects in three patients who received fairly large doses of roentgen therapy. However, they state that 1,000 to 2,000 r to the skin can cause no unexpected late results.

TABLE I. FOLLOW-UP SURVEY OF 349 CASES (TEN-YEAR PERIOD 1941-1951)

	GOOD	%	FAIR	%	POOR	%
Lymphadenosis	141	74	32	17	18	9
Sinusitis	66	60	24	22	19	18
Asthma	11	69	3	18	2	13
Ear conditions Recurrent otitis media Diminished hearing "Running ears"	27	82	5	15	1	3
Totals	245	70	64	18	40	12
Number of cases of tonsillectomy before x-ray therapy						84
Number of cases with no tonsillectomy to present						195
Number of cases of tonsillectomy after x-ray therapy						70

I agree that every safeguard must be utilized, but it should be recognized that the dose administered in the average case is sometimes less than that given to many infants and children who are subjected to routine fluoroscopic examination at each office visit.

The situation has been aptly summarized by Ingram[103]: "The attitude of alarm which has been so commonly associated with the idea of radiation work can safely be discarded, provided it is replaced by one of healthy respect for protective rules."

RESULTS

From January to March, 1951, a follow-up survey was made by questionnaire on 500 of the children treated with x-ray therapy during the

*Dr. Mendel Jacobi, formerly Director, Department of Pathology, Beth-El Hospital.

S. and M. G. Male Twins. Aged 6½ years.

History: Twin boys with almost identical history. Frequent colds since birth; cough all winter; frequent "abscessed" ears.
Examination: Purulent rhinitis, much lymphatic hyperplasia. (M. G. bilateral OMPC.)
Result: After x-ray therapy they improved tremendously, gaining over 8 pounds each in the next year.

H. F. Male. Aged 7 years.

History: Frequent colds with fever and croupy cough. Marked purulent rhinitis. T and A at 1 year. Had 20 bronchoscopic drainages for early bronchiectasis with very little improvement.
Examination: Purulent rhinitis; lymphoid tissue in pharynx, throat, cervical glands. Chest full of rhonchi, râles.
X-rays: Sinusitis severe. *Result:* After x-ray therapy, sinusitis cured, cough disappeared, and chest has cleared up.

W. H. Male. Aged 5 years.

History: Mouth breathing with dyspneic retractions. Severe hacking cough. Snores loudly even during day.
Examination: Purulent rhinitis. Tremendous tonsils. Chest: Rhonchi.
X-rays: 11/1/45. Right maxillary and ethmoid sinusitis.
Treatment: Course of x-ray therapy. *Result:* Snoring, cough gone. Breathing normal. Throat shows almost complete shrinkage of tonsils.
Recheck X-rays: 9/9/46. Sinuses negative.

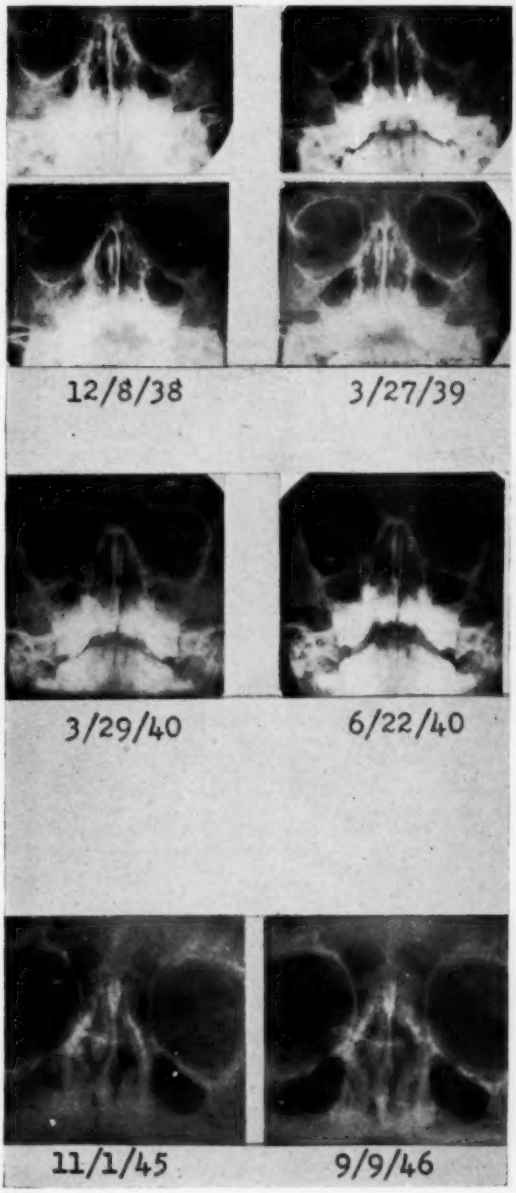


Fig. 2.

B. D. Male. Aged 6 years.

History: Marked malnutrition. Frequent colds with cough.
Examination: Hypertrophied. T. and A.
X-rays: Maxillary sinusitis. Ethmoiditis.
Result: X-ray therapy. Child did very well. Gained 14 pounds in 2 years.

I. B. Male. Aged 9 years.

History: Headaches, pains in face, stuffed nose, cough for past 3 winters.
Examination: Purulent rhinitis. Granular pharyngitis.
X-ray: Marked clouding of right antrum 5/11/47.
Treatment: 8 treatments. *Result:* Much improved. X-rays negative 1/21/48. Seen last 10/4/50, no recurrence.

G. P. Female. Aged 10 years.

History: Chronic purulent nasal discharge. Cough persistent—paroxysmal. Frequent acute colds with fever. T and A at 6 years.
Examination: Tenderness over left antrum. Granular pharyngitis.
Result: After x-ray therapy child had one slight cold the following winter. Otherwise has been quite well.

N. R. Male. Aged 3 years.

History: Cough 4 months with asthmatic bronchitis. Frequent colds in past. T. and A at 2 years with no improvement at that time.
Examination: Granular pharyngitis, cervical adenitis, severe bronchitis with wheezing.
X-ray: Marked sinusitis.
Result: After x-ray therapy, marked improvement though child has had occasional mild attacks. Gained 6 pounds in 9 months.

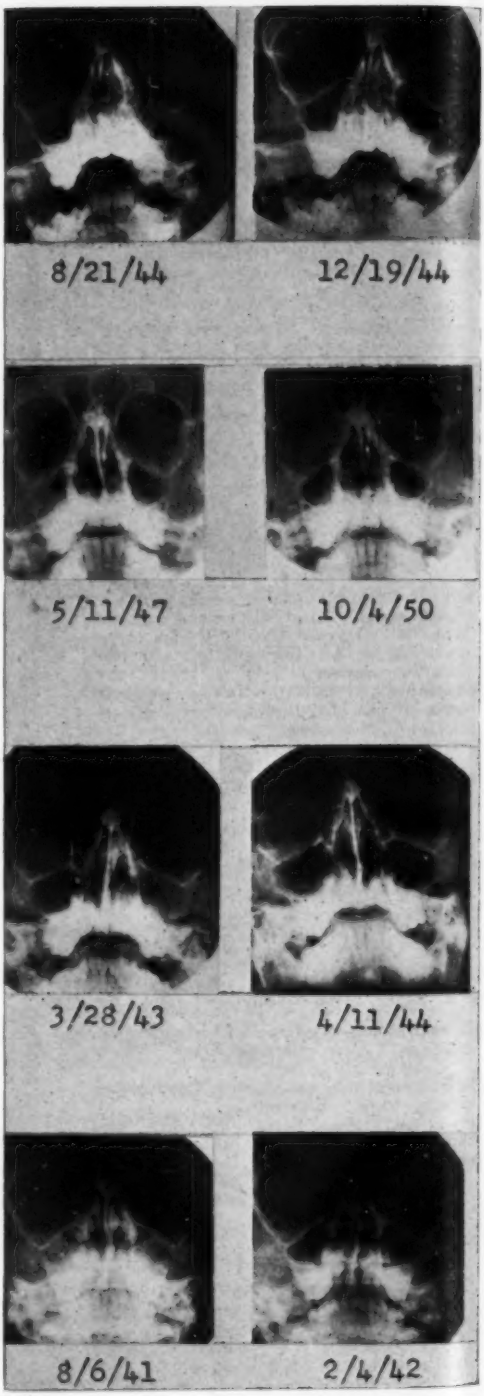


Fig. 3.

W. G. Male. Aged 7 years.

History: Chronic nose and ear discharge with many repeated colds. Fever and cough with each attack.
Examination: ROMPC. Purulent rhinitis; granular pharyngitis; bronchitis severe.
X-rays: Upper roentgenograms demonstrate sinuses before and after therapy. There is marked maxillary clouding with improvement on the follow-up film. Lower roentgenograms demonstrate shrinkage of the adenoid which is marked by the arrow.
Result: Ear cleared up promptly. No further colds or nasal discharge.

P. S. Female. Aged 3 years.

History: Repeated sore throats and nasal discharge for one year; sneezing. Allergic family history.
Examination: Purulent rhinitis—large tonsil and adenoid.
X-rays: 11/22/49. Bilateral maxillary clouding.
Treatment: 5 x-ray treatments. *Result:* X-ray 1/23/51—improved. Purulent discharge has not recurred in 14 months. Still some sneezing (under care of allergist).

I. S. Male. Aged 8 years.

History: Frequent attacks of upper respiratory infection with marked nasal discharge. Present attack 2 months with no response to usual treatment to the nose. Right sinus drained and irrigated with improvement for 2 days.
X-ray: 6/4/46. Opacity right maxillary and right ethmoid.
Treatment: X-ray therapy to sinuses. *Result:* Cessation of discharge after third treatment. Entirely well since.
Recheck X-ray: 9/22/46. Sinuses normal.

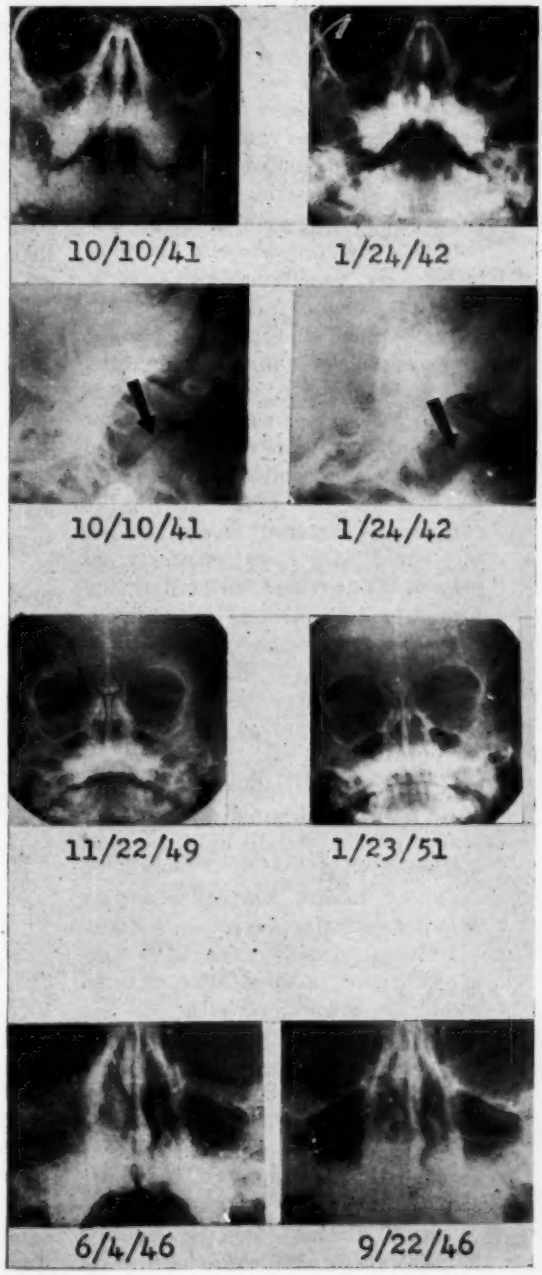


Fig. 4.

preceding ten years. These cases were chosen at random and it was suggested that the children be brought for re-examination whenever possible. Three hundred forty-nine responded, and the results are tabulated in Table I. Many of these patients had two or more conditions simultaneously but only one category (usually the most troublesome condition) was used to avoid confusion.

These results generally parallel previous surveys in the literature. Williams and Bryan[5] reported approximately 80 per cent cured, 10 per cent improved, and 10 per cent unimproved in cases of bronchitis, sinusitis, and rhinitis.

Firor and Waters[104] reported 34 per cent cured, 38 per cent markedly improved, 13 per cent moderately improved, and 15 per cent no results.

Butler and Woolley[9] reported their cases of sinusitis to be 33 per cent symptomless, 41 per cent improved, 26 per cent unimproved after roentgen therapy.

McLendon and Rathbone[13] reported 50 to 60 per cent cured, 30 to 40 per cent improved, and 10 to 20 per cent not improved.

Laing[14] treated 900 children with sinusitis reporting 71 per cent cures.

Hull and co-workers[73] in 1,500 cases of asthmatic sinobronchitis reported results as follows: excellent 39 per cent, good 40 per cent, fair 13 per cent, poor 6 per cent, no results 2 per cent.

After treating 257 cases of diseased tonsils, Schulte[36] reported 90 per cent cured, 6 per cent improved, and 4 per cent not improved.

Torres-Carreras[35] similarly reported 90 per cent of 147 children to have permanent improvement.

Brown, Titche, and Lawson[105, 106] reported 110 cases of various types of otitis media with excellent results in all.

The disparity in some of the statistics is undoubtedly due to the difficulty of assaying clinical results, but the over-all conclusions are similar—that in carefully chosen cases radiation is of great value.

A few of the typical cases with history and before-and-after roentgenograms are to be found in Figs. 2 to 4.

SUMMARY

1. Radiation therapy is a valuable adjunct in the treatment of sinusitis and lymphadenosis (chronically infected hyperplastic lymphoid tissue of the Eustachian tube, pharynx, adenoid, tonsil, cervical and perihilar glands) in childhood.

2. Sinusitis is frequently overlooked as the basic focus of infection in recurrent or chronic infections of the ear, nose, throat, or chest in children. Asthma is frequently the result of sinusitis.

3. Radiation therapy is specially indicated:

(a) For hypertrophied tonsils and adenoids in the young child.

(b) In cases of diminished hearing due to Eustachian tube obstruction.

(c) In the chronically ill child.

(d) In the presence of active infection or epidemics of poliomyelitis.

4. A follow-up of 349 cases (a total of 1,400) treated by me over a ten-year period is summarized. The results were 70 per cent good, 18 per cent fair, and 12 per cent poor.

5. There is no danger whatever in competent hands in the dose range recommended.

The author wishes to express his gratitude to the late Dr. Abraham Litvak, who was Director of the Department of Pediatrics, and who helped in many ways with the original plans of this work. Great indebtedness is also due to Dr. Bela Schick, Active Consultant to the Department of Pediatrics, for numerous valuable suggestions. Dr. H. I. Teperson, head of the Department of Radio-Therapy, was most magnanimous with technical advise and permission to use the facilities of his department. Many thanks are due to Miss Lillian Goodman and to Miss Anne Howe who gave many hours of very capable assistance as technicians rendering roentgen therapy to the patients in this study.

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Clinical Conference

CLINICAL CONFERENCE AT THE LOS ANGELES CHILDRENS HOSPITAL

MERL J. CARSON, CHIEF-OF-STAFF

Case 1. Concomitant Tuberculosis and Pemphigus. Treatment With ACTH

DR. LIM WAN NGO (Pediatric Resident).—S. W., a 19-month-old white girl, was admitted Feb. 17, 1950, because of an enlarged abdomen of uncertain duration. There were no gastrointestinal or genitourinary symptoms. Just prior to admission she developed a cough and listlessness. The previous history and family history were noncontributory. There were no siblings.

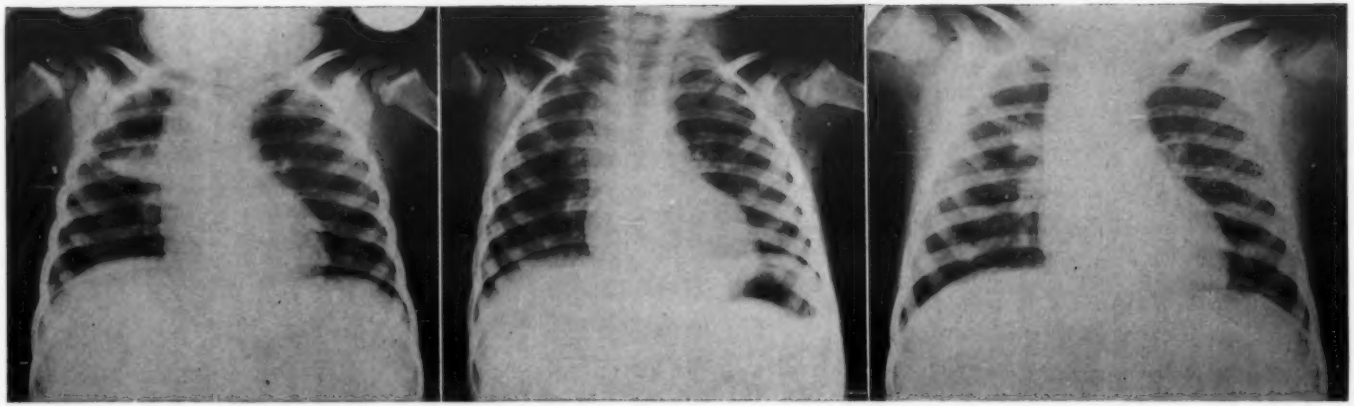
Physical examination revealed an apparently well girl with a temperature of 99° F. Plotted on the Wetzel grid she was in the A_6 channel and on the premature auxodrome. Her abdomen was distended but otherwise completely normal. The remainder of the examination was negative.

Laboratory findings included hemoglobin, 8.7 Gm.; red blood count 4.1 million, white blood count 6,400, with 60 per cent polymorphonuclears, 34 per cent lymphocytes, 5 per cent monocytes, and 1 per cent eosinophiles; erythrocyte sedimentation rate 23 mm. in one hour; negative urinalysis and Kahn; and positive Mantoux. A chest x-ray revealed a density in the right mid-lung field suggesting primary pulmonary tuberculosis (Fig. 1*A*). X-ray of the abdomen was negative. Cerebrospinal fluid was normal. Gastric washings, spinal fluid, and bone marrow were negative for acid-fast bacilli. Coccidioidin and histoplasmin skin tests were negative. The child's mother was found on routine x-ray to have active pulmonary tuberculosis with cavitation.

The abdominal enlargement could not be satisfactorily explained. No fluid was obtained on paracentesis. There was no laboratory evidence of hepatic or renal disease, abdominal tumor, or celiac disease. It was thought that the abdominal enlargement was probably of no significance. During the next two and one-half weeks her pulmonary tuberculosis improved spontaneously, and no specific therapy seemed indicated.

On March 7, eighteen days after admission, she developed vesicular lesions on her face, inguinal regions, and soles. Within twenty-four hours the vesicles became bullae and her temperature rose to 104° F. No source of infection could be found. Cultures of skin lesions and blood were both negative. Animal viral studies on fluid from the bullae were negative. With parenteral penicillin therapy she improved and became afebrile in a few days. The lesions began to dry and became crusted. On March 14, nineteen days after the administration of gamma globulin, given because of exposure to measles, she developed an attenuated case. This subsided in a few days.

From the Department of Pediatrics of the University of Southern California Medical School and the Los Angeles Childrens Hospital.

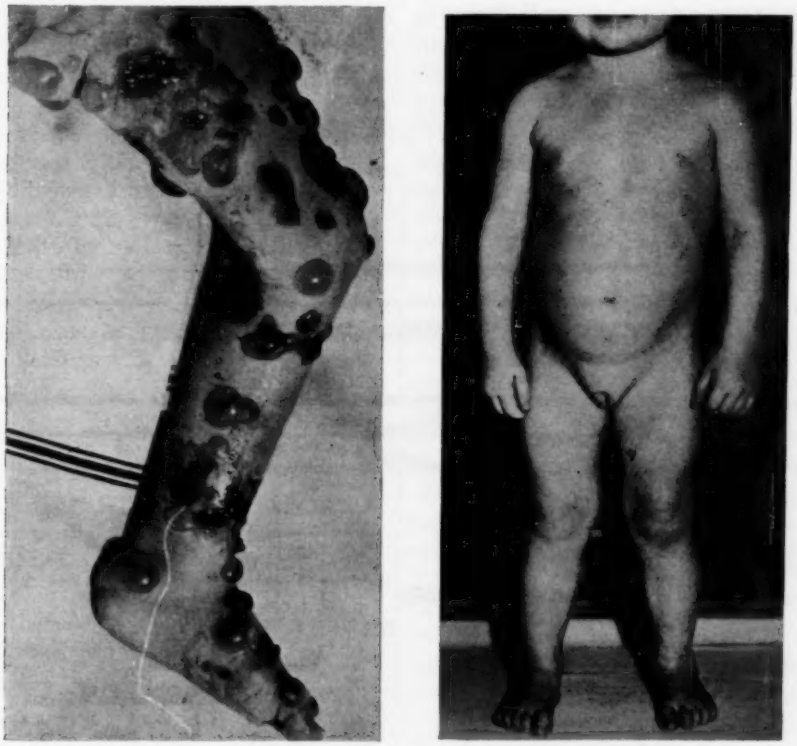


A. *B.* *C.*

Fig. 1.—*A*, Chest x-ray, Feb. 18, 1950. Pulmonary tuberculosis. *B*, Chest x-ray, March 23, 1950. Improvement in tuberculous lesion before streptomycin therapy. *C*, Chest x-ray, Nov. 30, 1950. Follow-up film showing further improvement following streptomycin therapy and course of ACTH for pemphigus.

On March 20, her temperature rose to 106° F. and she looked acutely ill. The only positive physical findings were a slightly tender and distended abdomen and a few dried bullous skin lesions. Her white blood count was 23,250 and her sedimentation rate was 78 mm. Blood culture, paracentesis, and cerebrospinal fluid were negative. A repeat chest x-ray revealed no significant change (Fig. 1*B*). A repeat Mantoux was strongly positive with a local bullous reaction. It was thought she had a dissemination of her tuberculosis, so penicillin was discontinued, and, on March 24, a three-month course of streptomycin, 0.5 Gm. daily, was begun. Within four days her temperature had fallen to 100.5° F., she appeared less ill, and the abdominal tenderness had subsided.

On March 28, new bullous lesions appeared on the skin of her face, trunk, and extremities (Fig. 2*A*). There were a few lesions on the buccal mucosa, but none on the conjunctivae. The individual lesions were identical in their evolution from vesicles to bullae. The surrounding skin was normal. Some lesions became hemorrhagic while a few became mildly infected. Nikolsky's sign was positive.



A. *B.*

Fig. 2.—*A*, Bullous lesions of skin prior to treatment with ACTH. *B*, Same patient following treatment with ACTH.

Healing occurred without pigmentation, scarring, or lichenification. There was no tendency to appear in crops. This process persisted for the next three months, during which time she had low-grade fever to 101° F., anorexia, slight weight loss, and pronounced lassitude. Mild pruritis developed after a month, but was relieved somewhat by oral Benadryl. Moist saline compresses and potassium permanganate dressings kept secondary skin infection at a minimum. She was given penicillin for about a month of this time. During this three-month period her sedimentation rate remained between 23 and 33; her white blood count rose to 39,000 and then fell to 16,000; her eosinophiles rose to 40 per cent or about 7,000 per cubic millimeter; and her serum proteins changed from albumin 4.5 and globulin 1.2 Gm. per cent, to albumin 2.2 and globulin 2.6 Gm. per cent. Examination of fluid from a bulla revealed a number of eosinophiles.

A skin biopsy revealed separation of the epidermis between the cornified and Malpighian layers. Some of the basal cells appeared edematous. The papillary bodies were edematous and contained some necrotic tissue, along with numerous eosinophiles and some lymphocytes.

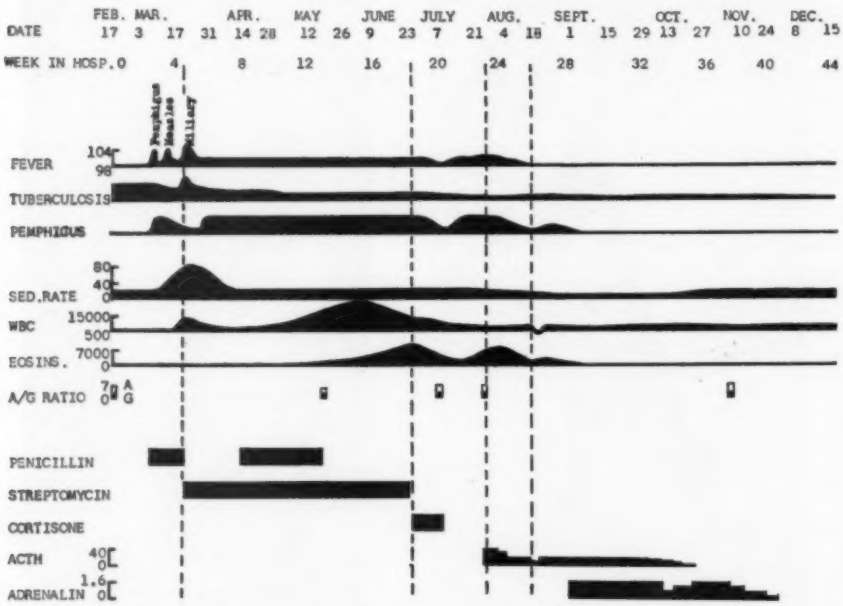


Fig. 3.—Chart of progress of patient in hospital, February to December, 1950.

Pemphigus was diagnosed, and, on June 28, after the completion of streptomycin therapy, a ten-day course of cortisone (30 mg. daily) was begun. Within five days her skin almost completely cleared and remained clear until a few days after cortisone was discontinued. Her temperature fell to normal, leucocytosis and eosinophilia diminished, and her serum proteins

changed to albumin 4.4 and globulin 2.0 Gm. per cent.

On July 26, when her pemphigus was in full exacerbation, she was begun on ACTH 40 mg. daily (10 mg. q. 6 h.). Within one week her skin had cleared, fever subsided, and the eosinophilia disappeared. Reduction in dosage resulted in a temporary exacerbation three weeks after therapy was instituted. At a dosage level of 10 mg. daily her eosinophiles rose from 11 to 418, her leucocytes fell to 2,800, and one day later new bullae appeared. Increasing the ACTH back to 20 mg. daily produced another remission. In September, ACTH was reduced in conjunction with the administration of Adrenalin (0.4 c.c. 1:1000 q. 6 h.). ACTH was discontinued on October 23, and Adrenalin on November 27.

The patient remained well (Fig. 2*B*), her laboratory findings were normal, and her chest x-ray revealed further healing of the tuberculous lesion (Fig. 1*C*), as of January, 1951. A repeat Mantoux on December 4 was strongly positive, but no bulla appeared.

A summary of our patient's course is presented in Fig. 3.

DR. P. E. ROTHMAN.—True pemphigus so rarely occurs in children that the diagnosis is always viewed with suspicion. All diseases characterized by bullous lesions, especially dermatitis herpetiformis and erythema multiforme bullosum must be excluded. The cardinal manifestations in this case were the sudden appearance of tense bullae on a normal skin, involvement of buccal mucosa, absence of appearance in crops or at sites of predilection, lack of polymorphism, healing without any cutaneous residuals, unremitting course, and constitutional symptoms.

It is always of interest to observe the effect of a concomitant disease upon the course of a tuberculous infection. Satisfactory statistical proof that the common intercurrent infections exert an unfavorable influence on a tuberculous lesion is lacking. In general, the alterations in the clinical picture of tuberculosis are due to secondary, nonspecific factors. For example, the cough of measles or pertussis, the inadequate nutrition of poorly controlled diabetes, the decreased pulmonary circulation in pulmonic stenosis, or the softening of caseous areas and spread of bacilli by lymph in pneumonia may each contribute to the progression of tuberculosis. Rich[1] is perhaps a little reluctant to conclude that secondary factors alone are responsible, and it is admittedly possible that other mechanisms exist. In the case under discussion one must consider the effect of both the constitutional and the cutaneous manifestations of pemphigus. Rich has reported a case in which a tuberculous child burned his forearm and developed papular tuberculids only at the healed site. However, no cutaneous lesions of tuberculosis appeared in our case. On the contrary, the intradermal tuberculin tests produced a local bullous reaction.

Initially, our patient's temperature remained normal. Her first bout of fever was associated with the onset of pemphigus; the second with the onset of attenuated measles. The third episode of fever, during which she appeared critically ill, was accompanied by moderate abdominal tenderness, leucocytosis, and elevation of the sedi-

mentation rate. Largely because these changes occurred at a time when her pemphigus was inactive and because no other cause could be demonstrated, a miliary spread of her tuberculosis was feared. Streptomycin therapy was instituted, and there followed an apparent dramatic response with immediate clinical and laboratory improvement, despite the fact that new lesions of pemphigus occurred and persisted with intense activity during the entire three months of streptomycin therapy.

If the diagnosis of an extension of the tuberculous process was correct, it could be attributed theoretically to the pemphigus, the attenuated measles, or the natural progression of tuberculosis. In respect to pemphigus any possible adverse effect disappeared with the use of streptomycin. In respect to measles any effect must be attributed to the disease per se, since no cough was present. We are in the dilemma of Dr. Toomey in his review "Does Pertussis Activate Tuberculosis?",[2] in which his initial case suggested that pertussis had contributed to, or had excited, a tuberculous infection. An analysis of nineteen additional cases convinced him that this is so rare that it was probably a coincidence. The observation of additional cases of pemphigus and tuberculosis is necessary before a conclusion is possible.

DR. A. G. KNUDSON, JR.—Of the patients we have treated so far with ACTH this little girl is probably the most impressive and the most gratifying. The very poor prognosis associated with pemphigus seemed to justify any reasonable therapeutic effort. ACTH was used empirically on the basis of a few reported successes with pemphigus.[3] The response of our patient to both cortisone and ACTH was prompt and unequivocal. Cortisone was replaced by ACTH because we feared adrenal atrophy with a prolonged course of cortisone.

Both drugs stopped the occurrence of new lesions immediately, and the old lesions healed about four or five days later. Her appetite improved, the fever subsided, she appeared more energetic, and seemed like a different child. At the same time, notable laboratory changes occurred, especially the disappearance of eosinophilia and the return of her serum proteins to normal.

ACTH produced no ill effects except that our patient developed a "moon-face," which regressed after cessation of ACTH therapy. There was no acne, hirsutism, hypertension, or glycosuria. Repeated electrocardiograms and serum electrolytes were normal. She was kept on a low salt, high protein diet and given 2.0 Gm. of potassium acetate daily. Her gradual weight gain was unassociated with edema. There was no apparent effect of ACTH upon the course of her tuberculosis, in fact healing progressed during the entire course of treatment. It is interesting to us that despite her exposure to the usual respiratory infections found on a children's ward, she never contracted one while receiving cortisone or ACTH.

The initial dose of ACTH was 40 mg. daily, or about 4.0 mg. per kilogram per day, divided into four doses. As soon as an effect was noticed this dose was tapered. Three days after the dose of 10 mg. daily was reached, her eosinophile count rose and her leucocyte count fell. The next day new lesions appeared. Reversal of these changes occurred when ACTH was increased back to 20 mg. daily. It was felt that the ACTH had so depressed her intrinsic ACTH production that

too rapid reduction of dose resulted in failure to stimulate the previously hypertrophied adrenals. We sought remedy for this by giving Adrenalin to stimulate intrinsic ACTH as our dose was again tapered. This time no exacerbation occurred.

While we are reserved with regard to the ultimate prognosis, we have some reason to be optimistic. Our current thought is that if ACTH does not cure a disease directly, it may at least protect cells from irreversible damage until such time as the disease becomes inactive. We would, therefore, not hesitate to institute another course of ACTH should exacerbation supervene.

QUESTION.—Do you have any ideas regarding the etiology of pemphigus?

DR. KNUDSON.—Much has been written about the etiology of pemphigus, but it remains unknown. Some favor a viral etiology, while others believe it may be a disease of metabolism. Possibly some type of sensitization such as occurs in rheumatic fever and the so-called collagenous diseases should be considered.

QUESTION.—Is there any rational explanation for the favorable response of pemphigus to ACTH?

DR. KNUDSON.—This has been an interesting subject to us. ACTH may operate beneficially in two ways. First, it may protect cells from damage as it does in rheumatic fever. Certainly ACTH has some effect on connective tissue as is shown by poor healing of clean wounds under its influence. Second, it may prevent the adrenal insufficiency which sometimes develops in pemphigus. As Goldzieher,[4] pointed out, distinct pathological changes occur in the adrenal cortex in patients with pemphigus. These changes progress from necrosis, atrophy, and lymphocytic infiltration to fibrosis and nodular hyperplasia. Gonadal atrophy may also occur. The common clinical findings of diminished urinary chlorides, decreased serum sodium and albumin, and eosinophilia together with the favorable response of some patients to adrenal cortex extracts or DCA indicate these changes are of functional significance. It is possible that pemphigus provides sufficient stress in Selye's sense of the word to exhaust the anterior pituitary-adrenal cortex system. Extrinsic ACTH could prevent this disastrous result.

Case 2. A Case of Idiopathic Hypoparathyroidism

DR. W. FRIEND (Pediatric Resident).—This white girl was first admitted to the Los Angeles Childrens Hospital at the age of 3½ years for study because of "cramping and drawing up of hands and feet" of three months' duration. She was the first-born of healthy young parents. Delivery at term was normal, her birth weight was 2,640 grams. There was no family history of hereditary or metabolic disorders. Two siblings, aged 2 years and 11 months, were living and well. The child was apparently well until three months before admission when she had an episode of "cramping and drawing up of hands and feet." She was taken to another hospital where after a complete work-up she was discharged. No diagnosis was given the mother, however. She was then in apparent good health until six days prior to the first admission at this hospital when the symptoms recurred. She was then readmitted to the first hospital, but after five days was transferred here for diagnosis and treatment.

Physical examination revealed an irritable female child in no distress.

The skin and hair were normal. The eyes showed no cataracts. The upper central incisors were slightly notched. Lungs, heart, and abdomen were not remarkable. Neurological examination revealed normal reflexes. Positive Chvostek and Trousseau signs were elicited, however.

On admission the blood hemoglobin was 10.3 Gm., white blood count 8,900 with a normal differential. The Kahn, tuberculin, and urine were negative. Nonprotein nitrogen was 33 mg. per cent, calcium 7.8 mg. per cent, phosphorous 11.5 mg. per cent, and the alkaline phosphatase 6 B.U. The x-rays of the long bones were read as follows: "The long bones show a band of density at the metaphysis much like the deposit in lead or other heavy metal poisoning. This was most pronounced at the lower end of the femurs and at both ends of the tibias, fibulas, radii, and ulnae." Electrocardiogram revealed a prolonged QT_c interval of .432.

The morning after admission the child suddenly developed carpopedal spasms (Fig. 4). After 7½ c.c. of calcium gluconate intravenously she relaxed completely. Three days after her admission with diagnosis of probable hypoparathyroidism, she was started on a regimen consisting of a low phosphate intake, calcium lactate 1 Gm. three times daily, and Amphojel 15 c.c. three times a day. On this regimen no relief was obtained. She had episodes of tetany each relieved by intravenous calcium gluconate (Chart I). Sixteen days after admission she was started on 2 c.c. (1.25 mg. per cubic centimeter) AT_{10} daily, in addition to the oral calcium lactate and Amphojel. The Trousseau and Chovstek signs remained positive for six days after AT_{10} therapy was instituted and then became negative. The phosphorus dropped from 11.5 to 9.2, and the calcium rose but slightly to 8.2 mg. per cent. The previously negative urine Sulkowitch became positive. On the twenty-third hospital day she developed chicken pox and was discharged to her home to return after recovery from this infection. She was

Fig. 4.—Spontaneous carpopedal spasm before institution of therapy.

sent home on a daily maintenance dose of 1 c.c. of AT_{10}, oral calcium lactate, and low phosphate diet.

She was readmitted one month after her first admission. During her stay at home the urine Sulkowitch was consistently positive and there were no signs of tetany.

Physical examination on this admission was negative.

per cent over a fourteen-day period. Her AT_{10} was then increased to 1½ c.c. every other day which was sufficient to keep her in a good balance. She was then discharged to be followed in the Outpatient Clinic. There were no recurrences of spasm and her blood calcium ranged from 9.4 to 11.4 mg. per cent, and phosphorus from 4.9 to 6.4 mg. per cent (Chart I).

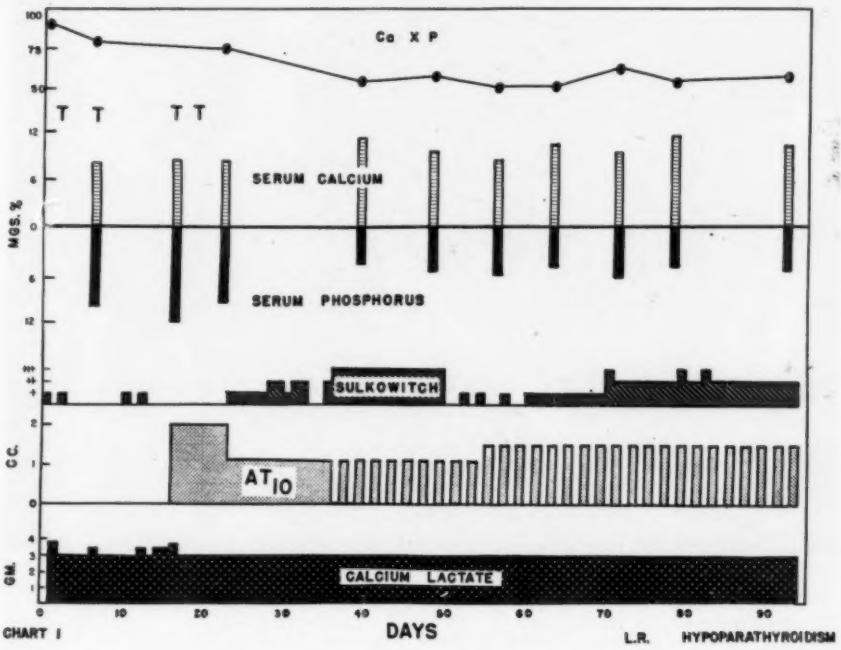


Chart I.—A composite chart showing the relationship of therapy to the serum calcium and phosphorus and the urinary excretion of calcium.

Laboratory data revealed a hemoglobin of 10.9 Gm., negative urine, calcium of 11.8 mg. per cent, and a phosphorus of 4.7 mg. per cent. Because of an increasing calcemia, the AT_{10} was reduced to 1 c.c. every other day and on this lowered dose her calcium dropped to 8.3 mg. per cent and her phosphorus rose to 6.1 mg.

Dr. G. Donnell.—Idiopathic hypoparathyroidism should be seriously considered in any apparently normal child who for no obvious reason develops clinical signs of tetany. The clinical and laboratory findings are so characteristic that there should be no difficulty in differentiating it from other causes of tetany. Rickets, renal

insufficiency and alkalosis can be ruled out by appropriate chemical studies. Pseudohypoparathyroidism presents a little more difficult problem since the clinical and laboratory features are identical. It differs, however, in etiology and in that these children exhibit certain characteristic structural changes. They are usually short, multiple trophic ectodermal changes are the most important ones described. These are apparently secondary to the lack of parathyroid hormone since they also occur following surgical removal of the parathyroid glands. The cause of the cataracts and metastatic calcification is thought to be the result of supersaturation of the serum with

Fig. 5. Fig. 6.

Fig. 5.—X-ray of the arm and forearm showing increased density at the distal end of the radius and ulna.

Fig. 6.—Roentgenogram showing increased density at the ends of the long bones of the lower extremities.

stocky, and have round faces. Shortening of the fingers and toes is common due to involvement of the metacarpal or metatarsal bones.

Other features not present in our patient have been described in hypoparathyroidism. The absence of these in our case is probably due to the short duration of her illness. Cataracts, metastatic soft tissue calcification, calcification in the basal ganglia, and calcium and phosphates. No explanation is at hand for the ectodermal changes. Confirmation of the clinical impression can always be obtained from the laboratory. A low serum calcium, diminished or absent urinary calcium (Sulkowitch test), an elevated serum phosphorus, and a normal or low serum alkaline phosphatase is to be expected, the degree of change reflecting the severity of the glandular

deficiency. The electrocardiogram is helpful in that it reflects the degree of hypocalcemia.

The bone x-rays (Figs. 5 and 6) in this child reveal an interesting and unusual finding not previously described in this disease. All the other reports mention a diffuse increase in the density of the bones. In this child, however, the increased density was limited to the metaphysis. This an area rich in phosphatase and phosphorylase. These enzymes act to increase the concentration of phosphate which further favors the precipitation of calcium salts. Since the epiphyses are the most rapidly growing portions, they might be expected to show the changes first.

Dr. M. J. Carson.—The purpose of treatment is to safely reverse the pathological process which has produced

Fig. 7.—X-ray of the chest. Note lack of increased density at the costochondral junctions.

brought up the question of heavy metal poisoning but no history or laboratory findings could be obtained to substantiate this. It is interesting to speculate on the cause of this change. If the products of the serum calcium and phosphorus are examined (Chart I), it can be seen that before treatment these values were one and one-half to two times the normal. This suggests a supersaturation of the blood with respect to some calcium phosphate salt, thus increasing the tendency for deposition of these salts in bone. The most logical site for this deposition would be the point of maximal growth, hypocalcemia. This can be accomplished in several ways. The action of parathyroid hormone is to increase urinary phosphate excretion resulting in a decrease in serum phosphate with a corresponding rise in the serum calcium. It would seem that the natural hormone would be the logical preparation to use. Unfortunately, after prolonged administration of parathyroid hormone, antibodies develop which result in a resistance to its action. Two other effective substances are available. Vitamin D and one of its irradiated derivatives, AT_{10}, both promote calcium absorption as well as phospha-

turia. The former action predominate with vitamin D and the latter with AT_{10}. The action of AT_{10} resembles the natural hormone more closely and is, therefore, more efficient. It is administered until adequate blood calcium levels are obtained. This can be gauged by the urinary excretion of calcium using the Sulkowitch test. Light precipitation indicates too little AT_{10}; heavy denotes too much AT_{10}. In addition to AT_{10}, an adequate supply of calcium should be furnished. Calcium lactate in doses of 1 Gm. three times a day is usually sufficient. The absorption of phosphate can be decreased by limiting it in the diet, especially by eliminating milk, and by administration of aluminum hydroxide. This child was started (Chart I) on 2 c.c. (2.5 mg.) of AT_{10}. On this regimen the serum calcium rose and the phosphorus decreased. Because of hypercalcinuria, the amount of AT_{10} was decreased to 1 c.c. daily and later to 1 c.c. every other day. This was not sufficient to maintain normal calcium and phosphate levels and it was not until the dosage was again increased that proper balance was established.

QUESTION.—Is the electrocardiogram of clinical value in the diagnosis of hypocalcemia or just of academic interest?

DR. C. BAKER.—Electrical systole is increased in certain electrolytic deficiencies. This period can be measured by the QT_c of the electrocardiogram. In hypopotassemia, the prolongation is essentially in the T wave itself and is accompanied by flattening of this wave and the appearance of U waves. In hypocalcemia, the prolongation is in the RST segment and the T waves are of normal magnitude and contour.

In either deficiency the electrocardiogram may be the most accurate test since the intracellular or ionized value may be lower than the serum level. The electrocardiogram is, therefore, a valuable tool in judging electrolytic therapy.

This patient repeatedly showed a prolonged QT_c with a long RST segment, but with normal T waves, these findings are consistent with hypocalcemia.

QUESTION.—What is the prognosis in a patient treated for hypoparathyroidism?

DR. DONNELL.—It is impossible to make a blanket statement regarding the prognosis in these patients as few long-term follow-ups are available in the literature. The reports that can be found deal only with the diagnosis, treatment, and the short period of study after therapy has been instituted. Most of the cases were diagnosed late in the disease after many of the secondary changes had become manifest. This undoubtedly would have a bad influence on the prognosis. There is no reason to believe, however, that life cannot be maintained satisfactorily if the cases are diagnosed and treated early in the course of the disease. One point should be re-emphasized here. Management of these children should be carefully controlled since overtreatment is as dangerous as inadequate therapy. One has to be aware of the inherent dangers of producing hypercalcemia with too large doses of AT_{10}.

Case 3. Idiopathic Thrombocytopenic Purpura With an Unusual Complication

DR. F. P. KOCH (Pediatric Resident).—This 12-year-old Japanese girl

has been generally well until the onset of her illness one month prior to hospitalization. During this time she has noticed increasing bruising tendencies. In addition to the bruising, she noticed petechiae over the lower extremities and episodes of bleeding from the oral and nasal mucosa. There has been no joint swelling, aching, or abdominal cramps. Vaginal bleeding (menstruation?) occurred for the first time two weeks after the onset of her illness. Family history was negative for any hemorrhagic disease.

On admission to the hospital she was noted, on physical examination, to be an essentially normal child except for diffuse purpura. Several petechiae were noted over the oral mucosa and numerous ecchymoses and petechiae over both legs and elbows. Beginning adolescent changes of the genitalia were noted. There was tenderness on external rotation of the right leg. The reflexes were equal and active, there was no lymphadenopathy nor hepatosplenomegaly. Blood pressure was 128/80, temperature 99° F.

Laboratory findings included hemoglobin 11.7 Gm. per cent; red blood count 4.02 million per cubic millimeter; white blood count 4,900 per cubic millimeter; polymorphonuclears 48 per cent; lymphocytes 38 per cent; monocytes 14 per cent; platelets 3,500 per cubic millimeter; bleeding time greater than 15 minutes; coagulation time 2½ minutes; capillary fragility test positive by both positive and negative pressure methods. The urine had a grossly red color; pH of 7.0; four plus albumin, and red cells too numerous to count. A bone marrow aspiration was reported to show "abundant megakaryocytes with no evidences of neoplastic disease."

Because of the history of purpura, the absence of other clinical signs, the profound thrombocytopenia, the otherwise normal blood picture, the normal bone marrow with abundant megakaryocytes, a diagnosis of idiopathic thrombocytopenic purpura was made. The anticipated therapeutic program was to try the effect of (a few) blood transfusions, but if there was clinical progression of the disease to resort to splenectomy.

During the subsequent twenty days, despite minimal bleeding and no progression of the purpura, the patient complained increasingly of pain in the right hip, and numbness and paraesthesias down the posterior aspect of her right leg. The right patella and achilles reflexes were now absent; also there were similar complaints and findings in the left arm. During the last ten days of this period, she became increasingly listless and had transient episodes of comatose-like states. Because of the clinical deterioration of her general condition a splenectomy was performed. Prior to the operation the platelet count had been repeatedly below 10,000; by twelve hours postoperatively her platelet count was 20,000. However, within two hours of clamping the splenic pedicle, the bleeding time decreased from twenty-one to seven minutes and finally to two minutes. During the next twenty-four hours, there was no further rise in platelets, and despite a general improvement in her appearance, there was a return of nasal and vaginal bleeding, and the bleeding time increased to twelve minutes.

Following surgery, there was a seventy-day interval during which her clinical condition remained unchanged.

She had repeated bouts of nasal and vaginal bleeding; twelve 500 c.c. whole blood transfusions were given, but there was no progression of the neurological signs previously mentioned. At the end of this period, all bleeding stopped, the platelets began to rise slowly from 3,000 in the course of twenty days to 84,000. During subsequent fifteen months, attention has been directed toward correction of the neuromuscular complications.

With final subsidence of the thrombocytopenia, examination revealed an emaciated individual, weighing 89 pounds, with flexion contractures of 45 degrees of both knees. There was complete paralysis of all muscles below the left knee and weakness of those of the right leg. Similar weakness to complete absence of muscle strength was present in both forearms. She was given extensive orthopedic care including traction to the legs followed by hydrotherapy and gradual weight bearing with crutches. In the first few months, there has been a return of most of the strength in all extremities so that she walks without crutches and is able to attend regular school; she has gained 20 pounds in the last year.

DR. P. STURGEON.—Most cases of idiopathic thrombocytopenic purpura in children seen in this clinic follow a very benign course with a spontaneous remission within a few weeks from the onset. A small percentage relapse but usually this is less severe and of shorter duration than the original episode. An occasional case has a fulminating onset and after a few days becomes much worse. It is this group of critically ill almost terminal patients who offer the greatest therapeutic difficulties. This type of material has been noted in the past, as in this case, in individuals with early signs of puberty.

One should anticipate that splenectomy in this group will decrease the prolonged bleeding time but may not necessarily result in a prompt return of platelets. In a previous case this was delayed as long as eighty days; but the prolonged bleeding time and clinical purpura improved considerably postoperatively. On occasions, splenectomy has been performed and followed by complete disappearance of the clinical purpura, and the individual subsequently leads a normal life. A previous patient followed in this clinic had a normal pregnancy and an uncomplicated delivery, despite the fact that her platelets never returned to over 20,000 per cubic millimeter postsplenectomy. Incidentally, the child born to this mother had typical thrombocytopenic purpura that cleared up in three to six weeks.

The postoperative course of the patient presented today and the course of the group just mentioned lend strong support to the theory that the spleen is more closely related to capillary contractility in the control of hemorrhage and that abnormality in platelet production is not a manifestation of splenic dysfunction. Splenectomy, therefore, should be looked upon as a procedure which corrects at least one of the abnormalities present in this disease (prolonged bleeding time) but not necessarily to control the thrombocytopenia.

The most serious complication of thrombocytopenic purpura is cerebral hemorrhage. Other complications include bleeding from the oral and nasal mucosa, genitourinary tract bleeding,

vaginal and gastrointestinal bleeding. This patient had several of these more common complications but is remarkable in that the neuromuscular complications and their subsequent improvement point strongly to diffuse hemorrhages in the vicinity of the peripheral nerve trunks and plexuses supplying the extremities.

QUESTION.—Were other bone marrow aspirations performed, and what did they show?

DR. STURGEON.—Four aspirations were performed in all; the megakaryocytes counts were 334, 297, and 164. Average normal by this technique is 137. In one instance, the specimen clotted so no megakaryocytes were seen. None of the aspirations showed any changes suggestive of leucemia.

QUESTION.—What is the prognosis?

DR. STURGEON.—The child's platelet count on last visit approximately fifteen months postoperatively was over 400,000 per cubic millimeter. So we do not anticipate any recurrence of the disease.

QUESTION.—Could the neuromuscular complications be attributed to central nervous system hemorrhages rather than peripheral involvement?

DR. F. ANDERSON.—I believe the lack of involvement of both legs simultaneously and the similar findings in the upper extremities indicate peripheral nerve pathology. Her subsequent recovery is also more compatible with this.

QUESTION.—Was toluidine blue medication used?

DR. KOCH.—Yes. Approximately one month postoperatively, the patient was given 100 mg. of toluidine blue intravenously daily for three days. At that time, her platelet count was less than 10,000 per cubic millimeter. Her general condition was very poor and remained so during, and many days subsequent, to the toluidine blue.

Case 4. An Unusual Case of Calcium Oxalate Deposits in the Kidney of a Young Infant

DR. MARY MULLOY.—D. B., a 4½-month-old male infant, was admitted to the private service* of the Childrens Hospital of Los Angeles in March, 1949. Convulsions of one day's duration had been noted. The birth weight was 3.5 kilograms, and the baby had been breast fed until ten days before admission. The vitamin intake had been adequate; 1 drop of Cecon and 10 drops of Abdec were given daily. At 6 weeks of age a pyloroplasty was done at another hospital; recovery was uneventful and thereafter the infant gained well up to 5.9 kilograms. Ten days before entry, vomiting after each feeding occurred with a weight loss of half a kilogram, and various formulas were tried. The day before admission the baby convulsed after each feeding, and twitching of the face and the right arm appeared.

Physical examination revealed a thin but well-developed, pale, lethargic infant obviously under heavy sedation. The pulse was 100 and the temperature 101° F. The length was 64 centimeters (normal 65 centimeters), and the weight was 5.6 kilograms (normal 7.1 kilograms). No overt evidence of infection was found. The Chovstek was positive. There was no evidence of rickets. The kidneys could not be

*By courtesy of Dr. Robert Shirley and Dr. Donald A. Charnock.

palpated nor the liver or spleen. The blood pressure was 80/50, and the fundi were negative.

Laboratory studies were as follows: In the blood, hemoglobin was 8.4 Gm.; the platelets were normal; white cells, 19,800 with 41 per cent polymorphonuclears, 44 per cent lymphocytes, and 13 per cent monocytes. The blood Kahn was negative. The urine was clear with specific gravity 1.018, pH 7.5, albumin 3+, sugar 0; microscopic examination of the centrifuged specimen showed 5 to 8 white cells, and an occasional red cell per high-power field with no casts. The urine culture was essentially negative. Serum calcium was 6 mg. per cent and serum inorganic phosphorus 16.7 mg. per cent repeatedly. The alkaline phosphatase was 6.7 Bodansky units. The CO_2 combining power was 34 volumes per cent on admission and fell to 10 volumes per cent a week later. The blood nonprotein nitrogen was 136 mg. per cent and rose to 202 mg. per cent within a week. Spinal fluid was not under increased pressure; it was clear with 8 white cells per cubic millimeter; protein was 60 mg. per cent, sugar 83 mg. per cent, and chloride 652 mg. per cent.

On roentgen examination the long bones were found to be normal; the kidney shadows were not enlarged but were extraordinarily dense with what appeared to be an even, diffuse distribution of some radiopaque material, probably containing calcium. Cystoscopy revealed no abnormalities, and retrograde pyelography was within normal limits (Fig. 8).

A diagnosis of severe renal insufficiency and nephrocalcinosis was made. The clinical course was rapidly downhill, convulsions recurred, acidosis progressed in spite of attempts at alkalinization; the blood nonprotein nitrogen rose rapidly and death occurred two and one-half weeks after admission.

Present in this case were severe renal insufficiency and nephrocalcinosis without an obvious explanation of the underlying pathology. We felt that the calcification was due primarily to renal disease. Primary hyperparathyroidism was discarded since the serum calcium level was low, the longs bones appeared normal, and other metastatic areas of calcification were lacking. The possibility of secondary hyperparathyroidism with phosphorus retention in the blood and a lowered serum calcium would certainly focus interest on the parathyroid glands.

Nephrocalcinosis has been described in cases of pyelonephritis due to various organisms, such as *Staphylococcus albus, Escherichia coli, Pseudomonas aeruginosa,* and *Hemophilus influenzae.* In this patient there was no history suggestive of a persistent or recurrent urinary tract infection, the urine culture was negative, and retrograde studies demonstrated no genitourinary anomaly.

Butler, Wilson, and Farber described nephrocalcinosis in acidotic infants. The syndrome was characterized by persistent dehydration, acidosis, and hyperchloremia with adequately functioning kidneys. The history and the high nonprotein nitrogen exclude our patient from this category.

Renal calcification has been reported in infants with alkalosis, dehydration, and hypochloremia due to high intestinal obstruction. Our infant was operated on elsewhere for pyloric stenosis at the age of 6 weeks

and a pyloric tumor was found. Thereafter weight gain was adequate and no vomiting occurred until the onset of the present illness. Thus there is no apparent causal relationship between the pyloric tumor and the nephrocalcinosis.

Are the parathyroid glands abnormal?

DR. RALPH E. KNUTTI.—At autopsy the positive findings were limited to the lungs, the kidneys, and one parathyroid gland. Both lungs showed a focal acute bronchopneumonia.

Fig. 8.—Scout film and intravenous pyelogram of D. B., 4½-month-old infant, with nephrocalcinosis. The diffuse distribution of radiopaque material is evident; no evidence of urinary tract abnormality was uncovered.

The x-ray picture of a peculiar, diffuse density in both kidneys together with the clinical and laboratory findings did not fall into any of the ordinary classifications of nephrocalcinosis. Of most interest to us is the location of the radiopaque substance in the kidney and its chemical analysis. We hope the post-mortem studies of Dr. Knutti will clarify these points as well as the questions:

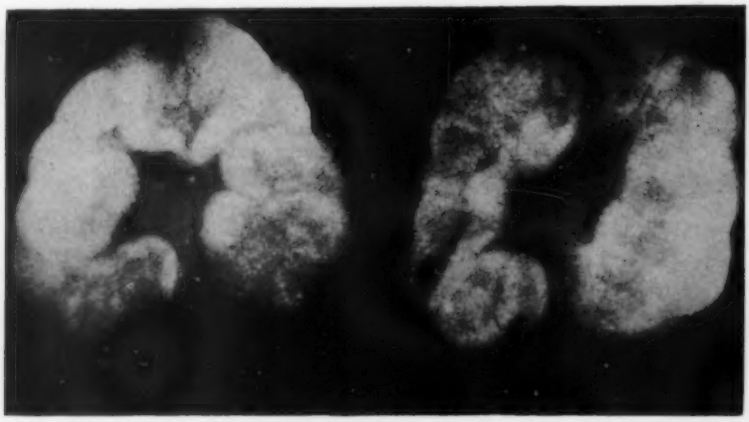
Is there any evidence of chronic pyelonephritis?

Both kidneys were normal in size and weight. The capsules stripped with ease and the cut surfaces appeared granular and were gritty when scraped with a scalpel. On microscopic examination the glomeruli seemed normal in size and distribution. Aggregates of peculiar transparent, yellowish crystalline material were noted within the collecting tubules and distributed about the proximal convoluted tubules. In some areas tubule structure seemed to have

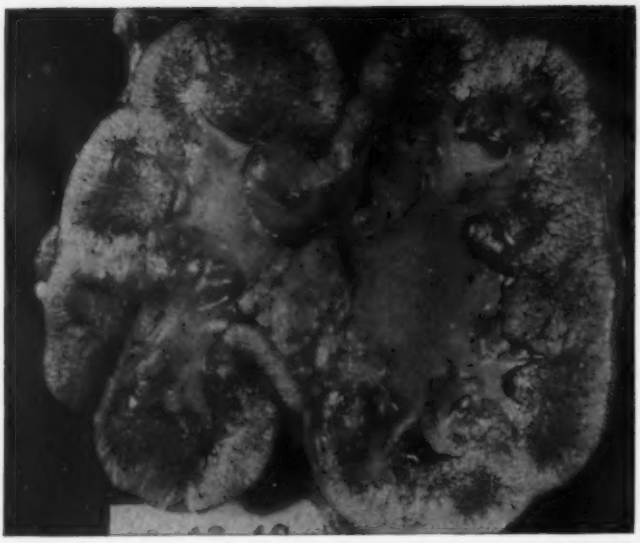
disappeared, and an increase of fibrous interstitial tissue was noted about crystalline material. When viewed through crossed prisms the crystals proved doubly refractile. With hematoxylin-eosin stain the crystals failed to stain blue as might be expected of the usual calcium salts. (Figs. 9 and 10.)

One parathyroid gland which measured 15 × 3 × 3 mm. was discovered. Microscopically this showed simple hyperplasia.

Quantitative chemical analysis of



A.



B.

Fig. 9.—Case D. B., nephrocalcinosis. *A*, Post-mortem roentgenogram of bisected kidneys. *B*, Cut surface of kidney showing finely stippled appearance of cortex and medulla.

the kidney tissue yielded 39 mg. of calcium per 1 gram of tissue.

X-ray diffraction of dried kidney tissue identified the calcium deposits as calcium oxalate monohydrate.

From the pathologist's standpoint, interest was added to this case because of the unusual appearance of the crystals in the microscopic preparations of the kidney. The clinical and x-ray diagnosis of "nephrocalcinosis," plus the autopsy finding of kidneys

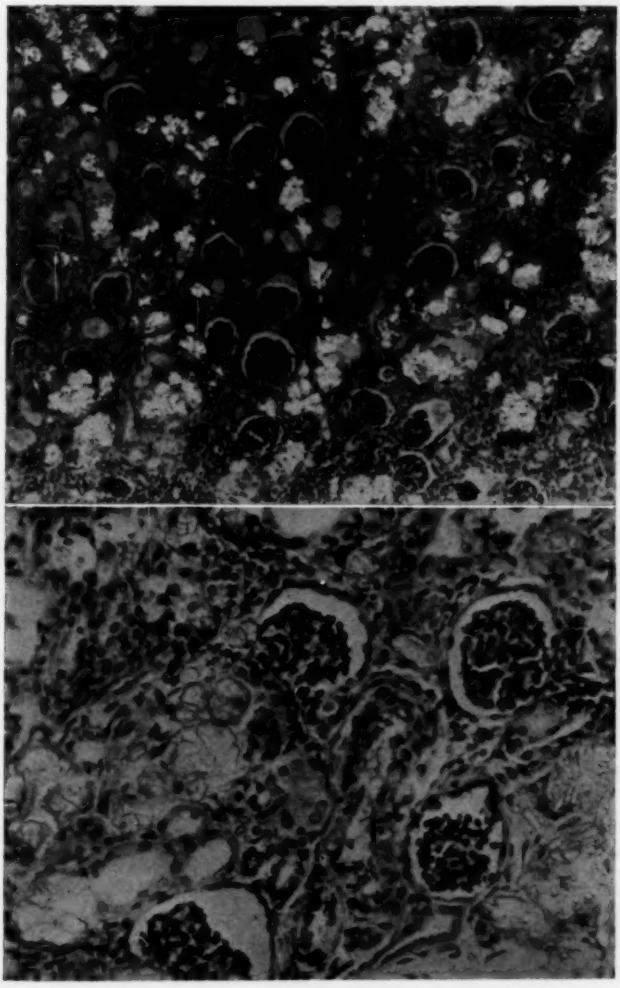


Fig. 10.—Case D. B., nephrocalcinosis. *A*, Photographed in partially polarized light, showing location of calcium oxalate (monohydrate) crystals. *B*, Hematoxylin-eosin stain showing the crystals in the tubules and interstitial tissue.

that grated on cutting, had prepared us to find blue-staining calcified material in the hematoxylin-eosin-stained sections. When the nonstaining crystals which were doubly refractile were observed under the microscope, we realized that we were not dealing with forms of calcium most frequently deposited in tissues as a result of chronic inflammation or degeneration, and the identification of calcium oxalate by x-ray diffraction confirmed this impression. Calcium deposits in tissues usually are composed of calcium phosphate, calcium carbonate, along with small traces of other substances.

Calcium oxalate crystals, however, are not uncommon in the urine of some patients, and their presence is often due to ingestion of various vegetables containing salts of oxalic acid (grapes, oranges, rhubarb, etc.), to drinking of carbonated water, or to ingestion of alkaline bicarbonates and various organic salts. Calcium oxalate crystals are said to be found in 25 per cent of urines that have been kept for twelve to twenty-four hours following urination. The deposition of calcium oxalate in renal tissue, however, is obviously quite rare.

Most of the reported cases of "nephrocalcinosis" containing calcium salts stain by the von Kossa method. A word about the von Kossa stain. In some publications it appears to be assumed that this is a microchemical technique which is specific for calcium, when, as a matter of fact, it actually shows up certain phosphates, soaps, and amorphous carbonates which might be combined with calcium.

Dr. Mulloy questioned the presence of chronic pyelonephritis. The absence of leucocytic infiltration would point against this condition. Although there is some increase in connective tissue about crystalline material, it might be considered that this is a reaction to the deposits rather than as a result of some specific infectious agent. As to the parathyroid glands, one was definitely enlarged, and microscopically showed simple hyperplasia.

The diffuse distribution of the deposits in the kidneys in this case is likewise quite rare and this is the first time that we have encountered it. Dr. Goettsch called my attention to the case reported by Vaughan and his associates[5] in which the arrangement was similar. This is the only other instance we have found in the literature.

DR. ELVIRA GOETTSCH.—This infant did not come to my attention until just before death. Clinically, renal insufficiency was readily apparent, but the startling feature was the evenly distributed radiopaque material dispersed throughout both normal-sized kidneys. Although the diagnosis of nephrocalcinosis was not difficult, we have not seen this variety before. Usually x-rays show conglomerations of calcified masses in the medulla about the pyramids, rather than such evenly distributed density. One can hazard the guess that because of its extent the calcification had been present for some time, possibly even in utero.

In this infant at 4½ months of age the serum calcium was depressed and the serum inorganic phosphorus markedly elevated; yet no lesions of osteitis fibrosa cystica were noted in the bones. It was evident that the pathologic process had progressed too fast to allow time for the development

of clinically apparent renal hyperparathyroidism.

We may expect pathologic calcification in normal tissues if abnormally high concentrations of calcium or phosphorus occur in the blood, and calcification may occur in injured tissues in the presence of normal blood levels of calcium and phosphorus. Abnormal calcification of tissues is most likely to be found where marked changes in pH occur or where increased concentration of phosphatase abounds. In the kidney tubules both of these requirements are found. In nephrolithiasis the concretions are commonly composed of mixtures of salts although calcium oxalate stones have been reported. The unusual location of doubly refractile crystals in the renal parenchyma of this infant, their uniformity and chemical identification as calcium oxalate monohydrate encouraged speculation as to a possible defect in metabolism, but to date all speculation has been fruitless.

In 1947, Vaughan and associates reported a case of nephrocalcinosis in an adult in which the x-rays resembled our case, although other features were quite at variance with our data. When the patient was first seen at 26 years of age, both kidneys showed diffuse calcification on x-ray. The blood phosphorus was 1.5 meq. per liter, blood calcium 4.6 meq. per liter, and the blood urea nitrogen 30 mg. per cent. According to the history, edema had first been noted six years previously. Almost two years later, just before death, the calcification of the kidneys had not changed appreciably although each renal shadow had decreased in size. The authors felt that the renal calcification was not the primary cause of the progressive renal insufficiency but merely a contributing factor.

At necropsy, microscopic sections showed calcified bodies throughout both the convoluted and collecting tubules of the renal cortex. These bodies gave a positive reaction when stained with von Kossa's stain. The medulla was free from calcification, and no calcified bodies were found in the pyramidal tubules. The chemical constitution of the calcified bodies was not determined.

Recently, in 1950, Davis, Klingberg, and Stowell[6] described a case of nephrolithiasis and nephrocalcinosis in an older child in which doubly refractile crystals presumed to be calcium oxalate were found at necropsy in both the kidneys and the bones. They felt that an unknown disturbance of the calcium or oxalate metabolism was probably the etiological factor.

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Psychologic Aspects of Pediatrics

RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

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NEW YORK, N. Y.

THE emotional implications of rheumatic heart disease in children have been discussed by Josselyn.[1] Her observations were made at a convalescent home. As psychologic hazards of the disease she mentions the physical incapacity during acute illness, often in a hospital for long periods with the consequent separation from home and family; the prolonged limitation of activity during convalescence, frequently in an institution; the threat of a permanent handicap. Even after convalescence the need for continued restriction of activity sets these children apart and deprives them of normal relationships with the group. In addition, death of a friend, from the disease which the child himself has, is highly disturbing.

A fairly large percentage of children with rheumatic fever react with a surprising capacity for adjustment. Nevertheless, the frequency of emotional disturbances is greater than in normal children but not more than in children with other chronic illness. The disturbance does not express itself in any characteristic pattern. The picture presented depends on the emotional state of the child prior to his illness. Some, but by no means all, of the disturbed children have shown evidence of poor adjustment previously. Many, however, had adjusted adequately and the breakdown takes place at the onset of the illness or during convalescence. Presumably emotional maladjustments, which were controlled under normal life circumstances, emerge when the strain of the illness is added. No sudden emotional upset was found to precede the first attack of rheumatism.

Josselyn observes that, even in those children where the adjustment to illness appeared to be a wholesome one, there was a tendency especially during early convalescence for the child to be more immature and more dependent upon adult relationships than would be expected in children of the same chronologic age.

Illness is frightening to the child, as it is to the adult, and hence anxiety is increased. The sick child tends to revert to a more infantile, dependent relationship with those caring for him. The emotionally healthy child finds solace and reassurance in the nursing care; and physicians and nurses become adequate substitutes for his parents. On the other hand, the child whose emotional development has been unsatisfactory comes to enjoy his dependency and to exaggerate his helplessness. Children with cardiac disease are prone to attribute any shortcoming in them-

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selves to the heart condition. Some of them establish the habit of evasion and self-indulgence. The general pattern of behavior has been described as the "only child complex," selfishness and dependence being prominent.

Another effect of the illness is that it interferes with the child's ability to assert himself in a healthy fashion. The normal child's self-confidence rests, in good part, on his opportunities for expressing his aggressive impulses. At the same time he is afraid of his aggression because an attack upon the situation he dislikes may lead to censure, disapproval, or punishment. The punishment may be loss of parental affection, an untenable situation for the young child. The child resolves his dilemma normally by physical activity and by directing his attacks against his peers and in active play. Rheumatic fever and rheumatic heart disease make this impossible.

A further blow to the psychic stability of the rheumatic child, associated with the need to limit activity, is the inability of the child to compete adequately in sports and the consequent undermining of his self-esteem.

It is Josselyn's opinion that, in a certain number of children the emotional state influences the symptomatology of rheumatic heart disease. She states that there have been several cases at Herrick House in which the most obvious explanation for increased symptoms seemed to be the child's anxiety. Other children showed surprising improvement when an underlying emotional disturbance was relieved.

Treatment.—The goal of treatment is to help the child to accept the limitations in activity imposed by his heart ailment. He should be encouraged to express his aggressive impulses through outlets which are physically safe. In addition he needs, when in a hospital or other institution, parent substitutes who can provide him with satisfactory emotional relationships. Later on it will be necessary for him to be weaned from his dependency on these parent substitutes. In this way he may discover that, in spite of his cardiac disease, the world is not as dangerous as it has seemed. According to Josselyn insight therapy is rarely necessary.

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News and Notes

The Pediatric Staff of the **Cook County Hospital** announces the third Maurice Lamm Blatt Memorial Fund lecture by Dr. Irvine McQuarrie, Professor and Head of the Department of Pediatrics, University of Minnesota, who will talk on "Clinical and Experimental Studies on Hypoglycemia." This lecture will be given Tuesday, Oct. 2, 1951 at 8:30 P.M. in the Medical Amphitheatre of the Cook County Hospital. All interested physicians are invited to attend.

At the annual meeting in May of the **Society for Pediatric Research** the following officers were elected to serve during 1951 to 1952.

President: Horace Hodes, New York

Vice-President: Howell Wright, Chicago

Secretary-Treasurer: Sydney S. Gellis, Boston

Members of the Council: Edward Pratt, New York, Nelson Ordway, New Orleans, and Charles May, Minneapolis.

The **American Board of Pediatrics** announces the following oral examinations:

Buffalo, N. Y., Oct. 26, 27, and 28, 1951

Chicago, Ill., early December, 1951

The following were certified by the **American Board of Pediatrics** at the examination held at Detroit, Mich, June 8, 9, and 10, 1951.

Dr. A. Maynard Bacon, Jr., 4619 Marble Hall Rd., Baltimore 12, Md.

Dr. George H. Becker, 210 Lister Bldg., 4500 Olive, St. Louis 8, Mo.

Dr. James Chester Beesley, 213 N. Broad, Lancaster, Ohio.

Dr. Leonard Bernard Bellin, 325 Angell St., Providence, R. I.

Dr. William A. Brodsky, School of Medicine, University of Louisville, Louisville, Ky.

Dr. Eunice Elizabeth Bryan, 19070 Ballinger Way, Seattle 55, Wash.

Dr. Louis G. Bush, 804 East Center St., Pocatello, Idaho.

Dr. Hugh H. Butler, 165 Shoreham Dr., Rochester 18, N. Y.

Dr. Ellsworth Ferrell Cale, 33 Ponce de Leon Ave., N.E., Atlanta, Ga.

Dr. George Gordon Cobley, Capt. MC 0-1921805, A.S.U. 117, USAH, Camp Edwards, Mass.

Dr. Quinten Wood Cochran, 4323 S.W. Hamilton Terrace, Portland 1, Ore.

Dr. Allan Bertram Coleman, 1433 Whittier St., N.W., Washington 12, D. C.

Dr. Thomas E. Cone, Jr., 108 North Stanworth Dr., Princeton, N. J.

Dr. Marvin L. Davis, 2 North Garfield Ave., Alhambra, Calif.

Dr. J. Frederick Eagle, Jr., 366 Lincoln Parkway, Buffalo, N. Y.

Dr. Marshall John Feeley, 505 Pleasant, St. Joseph, Mich.

Dr. Carolyn Wood Forman, 525 East 68th St., New York, N. Y.

Dr. D. Carleton Gajdusek, The Children's Medical Center, Boston, Mass.

Dr. Carl William Goebel, 213 W. Jefferson St., Ft. Wayne, Ind.

Dr. Marvin Harold Goodwin, 416 No. Bedford Dr., Beverly Hills, Calif.

Dr. Morris Green, Department of Pediatrics, University of Illinois, College of Medicine, Chicago 12, Ill.

Dr. Charles H. Hellmann, Professional Center, Glen Cove Ave., Glen Head, N. Y.

Dr. Louis Hodes, 444 Central Park West, New York 25, N. Y.

Dr. Clarence L. Hoogerland, 236 North State St., Alma, Mich.

Dr. Felix E. Karpinski, Jr., 2103 Adelbert Rd., Cleveland 6, Ohio.

Dr. Walter Richard Kessler, Babies Hospital, New York 32, N. Y.

Dr. Ruth F. Krauss, 111 Columbia Blvd., Kenmore 17, N. Y.

Dr. Sidney L. Lasell, 127 North Madison Ave., Pasadena 1, Calif.

Dr. Wayne E. LeBien, 1353 5th St. No., Fargo, N. D.

Dr. Felix G. Line, 710 West Hill, Knoxville, Tenn.

Dr. George Albert McCloskey, 197 W. Madison St., Rochester, Pa.

Dr. Lewis Meyers, 706 W. Kalamazoo Ave., Kalamazoo, Mich.

Dr. Thomas O. Middleton, 404 East Seventh St., Bloomington, Ind.

Dr. Harold R. Miller, 30 South Bellevue, Memphis, Tenn.
Dr. Howard H. Nichols, 1126 Winding Way, Nashville, Tenn.
Dr. Marvin Nierenberg, 6751 Jeffrey Ave., Chicago 49, Ill.
Dr. Raphael N. Paul, 188 South Bellevue Blvd., Memphis, Tenn.
Dr. Ralph John Pelegrin, 10515 Carnegie Ave., Cleveland 6, Ohio.
Dr. Donald Charles Phillips, Suite 529, Doneen Bldg., Wenatchee, Wash.
Dr. John Joseph Piel, 3641 California St., San Francisco 18, Calif.
Dr. Richard N. Reuben, 135 West 84th St., New York 24, N. Y.
Dr. Thomas F. Riedy, Jr., 5 Circle Lane, Albany, N. Y.
Dr. Nathan Schifrin, 888 Park Ave., New York 21, N. Y.
Dr. Warren Earl Shelden, 17300 Schaefer, Detroit 35, Mich.
Dr. Sheldon C. Siegel, 2154 Randolph Ave., St. Paul 5, Minn.
Dr. Viola V. Startzman, 421 N. Market St., Wooster, Ohio.
Dr. Donald Golder Stitt, 59 South Washington St., Waynesburg, Pa.
Dr. Dave Tobolowsky, 2406 South Blvd., Dallas, Texas.
Dr. Hyman C. Tolmas, 2049 Metairie Rd., New Orleans 20, La.
Dr. Robert Orr Warthen, 3 West Everett St., Kensington, Md.
Dr. Starks Johnson Williams, 1 North Western Ave., Chicago, Ill.

Book Reviews

Textbook of Pediatrics. Fifth edition. Edited by Waldo E. Nelson, M.D., Philadelphia, 1950, W. B. Saunders Co., 1,658 pages. Price $12.50.

This "fifth edition" bears little relationship in form or content to the original "Griffith edition" of 1933. As edited and revised by Mitchell in 1941, and particularly in the 1945 and present editions by Nelson, it has become one of the standard texts in pediatrics for use by medical students, and as a reference book for physicians in practice. It has won this position on its merits.

This "fifth edition" is a complete revision, and not just a reprinting with a few changes here and there for the publisher to establish a current dating. It has kept abreast of the many changes in pediatric thought and knowledge and the rapidly changing advances in medical science. To begin with, the new edition is larger than the last by over 300 pages or about 25 per cent. This makes it about the maximum size a single volume text can be used conveniently.

As the chapters are compared it is found that the sixty-odd contributors have as a whole thoroughly revised or completely rewritten the discussion of the subjects assigned to them. In addition, a number of new chapters have been added which round out the completeness of the text. Among these, the one on physical growth and development by Stuart and Stevenson is an excellent and thorough discussion of this subject which forms the *raison d'être* of pediatrics. Senn has taken over the chapter on psychologic disorders discussed by the late James Plant in the fourth edition, and has rounded out the chapter on adolescence by Johnston by adding a section on the psychologic aspects. The revision by Poncher and Unna of their chapter on drug therapy keeps it abreast of the rapid changes in this field in the last five years. These are but a few examples of the many important changes in the new edition.

The entire text has been carefully edited, and the English is clear and easy to read—the test of good writing. The reviewer who has been using the 1945 edition finds this new fifth edition a decided improvement, and a most satisfactory, well-rounded, and well-balanced text on pediatrics.

Nutrition and Chemical Growth in Childhood. Vol. III. Calculated Data. Icie G. Macy, Ph.D., Sc.D., Springfield, Ill., 1951, Charles C Thomas. Price $8.00.

This volume contains the detailed statistical data of the studies by Dr. Macy and her associates. It is of value to scientific workers making similar studies in the field of metabolism in children, but of little or no interest to the practitioner.

An Introduction to Universal Serologic Reaction in Health and Disease. Reuben L. Kahn, D.Sc., Oxford University Press, London; The Commonwealth Fund, New York, 155 pages. Price $3.50.

This new volume discusses a precipitation reaction which takes place between the serums of all human beings and animals thus far tested and tissue extract antigens. It represents a study, by the author of the Kahn test for syphilis, growing out of many years of experimentation to explain and control the occasional false positive reaction in this test for syphilis. No currently used test is completely free from this difficulty, nor has a satisfactory explanation for it been advanced heretofore. Dr. Kahn has used here an ingenious method of graphing the precipitation resulting from mixing and cold-incubating various serums and serum dilutions with standard Kahn antigen. More than 300 such graphs grouped in 113 charts are found within the pages of the book. By their aid, the situation is visualized as reaction is compared with reaction.

The author states with reference to the development of the universal serologic technique—(it) "may be said to have been in the process of evolvement in this laboratory during the past quarter of a century. We began to surmise soon after the development of our precipitation test for syphilis that positive reactions with this test are not limited to so-called true and occasional false positives; that positive reactions in the absence of syphilis may represent a unique and common biologic manifestation."

A standard technique has been worked out, by the application of which to serums of goodly numbers of both normal and diseased individuals, and of animals, data have been gathered and classified for this preliminary report. Quoting the author again: "The data herewith presented are in the nature of a preliminary report. The universal reaction has been investigated in this laboratory for over three years with limited facilities, while such a project requires ten years with extensive facilities. Yet it seems best to present the data available under one set of covers in order to facilitate their better correlation and to stimulate other investigators to confirm and extend these observations."

After an introductory chapter in which terms are defined and techniques described, two chapters are given to the reaction in normal individuals and the constancy of repeat tests in the same individuals. Then follows a chapter on the reaction in eight different kinds of animals, serums from half of which yield precipitation of such degree as to be read positive in the reaction for syphilis. The reaction in persons having syphilis, yaws, leprosy, malaria, and tuberculosis, respectively, is considered in the next five chapters. An analysis of data acquired from a group of institutionalized children provides subject matter for Chapter X, while XI is given over to some technical studies—variations of the standard technique used in the preceding studies. In the final chapter, the author discusses an hypothesis to explain—"How the same heart extract antigen can elicit different serologic patterns with serums from different diseases." Ample graphic data are given to demonstrate the universality of this serologic reaction with tissue extract (lipid) antigens such as the standard Kahn antigen. The same situation obtains in complement fixation tests, which are in fact precipitation tests upon which an hemolytic system is superimposed as an indicator. Use of red cells as indicator in the latter prevents varying the salt concentration to either side of the physiologic level; thus complement fixation techniques could not be utilized to study such facts as are presented here.

The format of the book is attractive. The wide page which accommodates chart and description side by side invites attention. The content is well organized and clearly presented by one especially experienced in the field.

This book will interest a wide range of scientists and is important reading to all in the special field of serology.

R. GERSTUNG

Editor's Column

POLIO PROBLEMS FOR THE PEDIATRICIAN

AS THIS issue of the JOURNAL appears we again enter on the polio season. Whether it will be another "epidemic year" cannot be forecast at the present time. As of July 1, the incidence this year has been lower than last year, and no epidemic tendency has been reported.

* * * * *

The most perplexing new problem for the pediatrician to ponder over is that of immunizations during the polio season. In the June issue (p. 781), the problem was discussed editorially by Robert Ward of New York. After summarizing published reports and unpublished studies, Ward came to the conclusion that "the present evidence seems clear enough to warrant the postponement of immunizations and other elective inoculations during the summer and fall months when poliomyelitis is likely to appear in epidemic form." This editorial, which was written late in April at the request of the Editorial Board, had scarcely reached JOURNAL readers when on June 12 and 13 news stories appeared in the *New York Times* which have led to the problem becoming known to the public almost before the majority of practicing physicians were aware that a problem existed.

On June 12 the New York City Health Department announced that it would suspend immunization against diphtheria and whooping cough in its seventy-six Child Health Stations in children over 6 months of age from June 15 to October 1, because of "a probable relation between immunization during the polio season and the localization of paralysis." The order was based on a preliminary report of a study which was started in March by the Department, as a result of the reports cited by Ward in his JOURNAL editorial. It is estimated that ordinarily some 25,000 children would have received injections during this period. The final New York City figures will not be available until the end of the year. It is obvious therefore that this preliminary report must have been of very definite statistical significance to have led the Health Department to take such drastic action.

The following day an announcement appeared that the New York State Health Department was sending out an urgent recommendation to physicians throughout the state that great care be used in *all* types of inoculations. The state bulletin includes not only diphtheria and whooping cough prophylactic immunizations, but according to the press announcement insists that the danger is implied in all kinds of injections, as, for example, penicillin.

In the June issue of the *American Journal of Public Health* a statement was published (p. 746) by the Committee on Research and Standards of the American Public Health Association, who referred the matter to a special *ad hoc* subcommittee as "the

problem was one of vital importance to the public health professions, not only from the viewpoint of prevention of poliomyelitis but also for the adverse effect any proven relationship might have on immunization programs against smallpox, diphtheria, whooping cough and others so much a part of today's public health."

The report of the special subcommittee, of which Gaylord Anderson was chairman, and among whose members were W. L. Aycock and Ralph Muckenfuss, was accepted by the committee. We quote the report of the subcommittee as it reflects the current opinion and attitude of public health workers and officials who are vitally affected by the issue.

"Recent published and unpublished data strongly suggest that an individual who develops poliomyelitis within a month after receipt of an injection of an antigen, or possibly of some other material, shows an increased frequency of paralysis in the extremity into which the injection has been given. There are also suggestions that among the reported cases of poliomyelitis are cases 'which would not have been clinically diagnosed as poliomyelitis at all if their (recent) inoculation had not brought them into the paralytic group.'

"Although further studies on these questions are imperative, the data so far available would suggest that, in the face of an abnormal prevalence of poliomyelitis in a given locality, antigen inoculations may well be postponed until after the subsidence of the abnormal prevalence. It should be stressed, however, that there is no evidence that this effect of inoculation persists for more than one month. On the contrary, the risk of poliomyelitis among persons who have been immunized more than one month before onset is no greater than among non-immunized persons."

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Thus the pediatrician is faced with a problem and a responsibility. For years the pediatricians and health departments have campaigned for immunization against diphtheria and whooping cough with the result that the first disease has largely disappeared, and the morbidity and mortality of the second has been greatly reduced. Now we turn and say avoid them during the polio season. It will be a difficult task to make the public understand that the immunizations and injections do not predispose a child to polio. We have already run into this problem from readers of the newspaper. It will take time and patience and the translation of a technical situation into common English to make parents understand the relationship that apparently exists between polio and injections, and that it is not one of cause and effect so far as contracting the disease is concerned. It will take a definite campaign of education to make parents understand the reason for suspending immunizations during the polio season, or the result will be a decrease in prophylactic immunizations with an increase in diphtheria and the severity of whooping cough. We must not lose what has been gained over the last twenty-five years because of the hysteria engendered by the recent polio campaigns.

For certain conditions and illnesses injections are imperative, and their omission is not justified because of the danger of localization of paralysis should the child develop polio. Tetanus toxoid following an injury, and insulin for the diabetic child are obvious examples. Parenteral fluids for dehydration in diarrhea, which has the same seasonal incidence as polio,

is another. Common sense would dictate that where the withholding of an injection endangers the recovery of a sick child, or increases the likelihood of death, it is not justified because of the remote possibility of poliomyelitis. The final responsibility rests on the judgment of the physician in determining the relative importance of the risks.

Seemingly the wise course for the practicing physician at present would be to postpone immunizations against diphtheria and whooping cough in children over 6 months of age during the summer months, until more pro or con evidence of the danger of injections is available. Further, some of the oral antibiotics might be substituted when possible for those administered by injection. Perhaps prophylactic immunization injections might be given at the fourth and fifth months of age if these fall in the summer months, and the completion be delayed until the following winter. Typhoid immunizations for campers next year might be given in May, rather than waiting until school closes in June, even if they upset to some degree the crowded spring period of the school year.

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To turn to another phase of polio. In this issue (p. 144) we publish a short paper on treatment in the acute stage of polio by Stimson, and a discussion of his paper by Hodes. These were presented in June at the meeting of the A. M. A., and permission to publish in the JOURNAL was kindly granted by the Editor of the *J. A. M. A.* This is the phase of polio therapy for which the pediatrician has great responsibility. While in large part the paper and discussion deal with the management of respiratory and swallowing difficulties based on the underlying physiology, there is one point raised that is seemingly quite in disagreement with the usual teaching in the medical schools. "Hospitalization is not necessarily essential. . . . Given favorable home circumstances, polio suspects, nonparalytic cases, and even minor paralytics can be diagnosed and cared for at home to the patient's distinct advantage." It is refreshing in this present-day era of unnecessary hospitalization of children, not only to the detriment of the family pocketbook but often to the welfare of the child, to find this statement made by someone whose work and experience with polio is well known and whose opinion on the subject carries authority. To rush a child to a hospital for a diagnostic lumbar puncture when polio is suspected is considered bad practice by many experienced physicians. As Stimson states, "The spinal fluid findings do not 'confirm the diagnosis' but may be 'consistent with the diagnosis of polio.'"

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In the May issue of the JOURNAL a detailed study of the relationship between poliomyelitis and tonsillectomy by Sigel, Greenberg, and Magee of the New York City Health Department was published. Based on a study of over 53,000 tonsillectomies during the epidemic of 1949 in New York City, the conclusion was reached that tonsillectomy predisposes to the development of clinical symptoms of polio. This confirms earlier studies. Although a few reports have failed to establish a re-

lationship, it is today generally accepted that a relationship exists, and that children who develop polio within a month or so following a tonsillectomy are predisposed to clinical symptoms, and a greater amount of paralysis, than nontonsillectomized children who develop the disease during an epidemic. For these reasons elective tonsillectomy should be postponed during the summer months. The 1949 epidemic in New York continued into mid-December, hence the authors considered that January, February, and March would have been the safest months in 1949 for elective tonsillectomy operations. These months, it is interesting to note, are the months that to some extent have been avoided in the past because of the danger of respiratory infections. This latter danger has, of course, been lessened since the advent of the sulfonamides and antibiotics. In a second article in the May issue by the same authors it was shown statistically that cases of polio developing shortly after tonsillectomy are predisposed to develop bulbar paralysis, with an increased fatality in cases occurring within two months following operation. The critical period was the first three weeks following tonsillectomy.

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Thus in addition to fatigue and tonsillectomy predisposing to the development of clinical symptoms and paralysis in a child who develops poliomyelitis, the latest is inoculations of one type or another. From a practical standpoint the problem of immunizations is a far more important issue than that of tonsillectomy for the pediatrician in practice.

B. S. V.